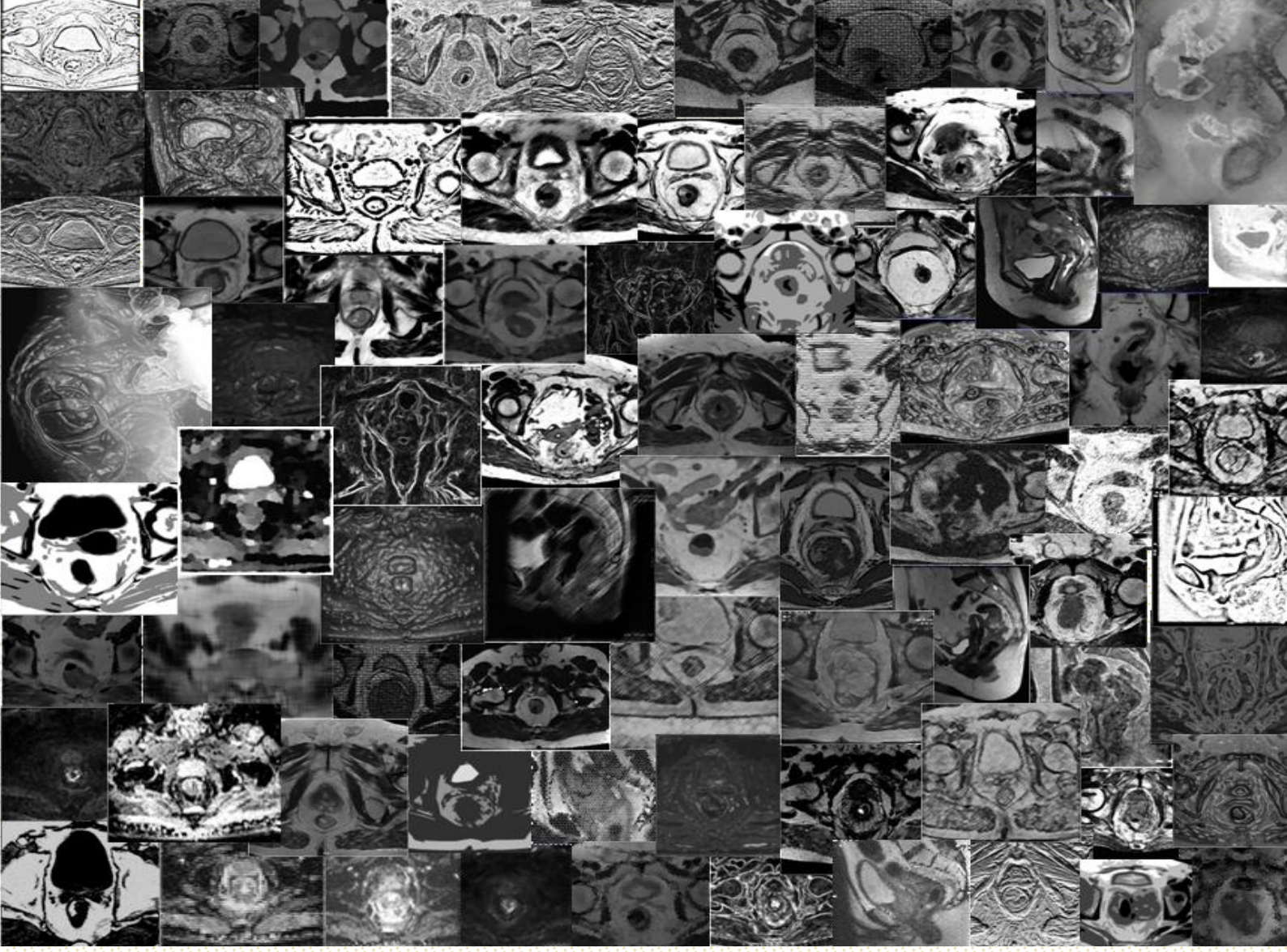

Luís Miguel Catarino Curvo Semedo

CURRENT CONCEPTS FOR IMAGING RECTAL CANCER

Dissertação de Doutoramento em Ciências da Saúde, no ramo de Medicina, na especialidade de Medicina Interna (Radiologia e Imagiologia) apresentada à Faculdade de Medicina da Universidade de Coimbra

Setembro de 2012

· U C ·

UNIVERSIDADE DE COIMBRA

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This work was held in the Clínica Universitária de Radiologia, Hospitais da Universidade de Coimbra, Portugal and in the Radiology and Surgery Departments of the Maastricht University Medical Centre, Academisch Ziekenhuis Maastricht, The Netherlands.

Dissertação de Candidatura ao grau de Doutor apresentada à Faculdade de Medicina da Universidade de Coimbra

To my Wife

To my Daughters

To my Parents

To my Brothers

To my Family

To my Friends

To Professor Filipe Caseiro Alves

To Professor Júlio Soares Leite

To my Masters

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Introduction

The imaging of rectal cancer has evolved considerably over the past two decades; there is a definite change in the imaging approach of this neoplasm. The methods of choice for imaging rectal cancer, in a pure morphological way, include endorectal ultrasound and magnetic resonance imaging. However, new imaging techniques for rectal cancer are emerging and others still evolving. Functional imaging through perfusion computed tomography or diffusion-weighted magnetic resonance imaging are now being increasingly used in clinical practice as additional tools with the purpose of helping to detect, characterize and stage rectal cancer (and also in the context of evaluating response to therapy and detecting local recurrence).

The purpose of this thesis is to show some of the experience of the Radiology University Clinic of the Coimbra University Hospitals in these fields of imaging. It is also seeks to demonstrate the expertise of the Radiology and Surgery Departments of the Maastricht University Medical Centre, where I was fortunate to work on a daily basis and where part of the clinical research was performed.

Thus, the subject of rectal cancer addressed herein will be divided into two parts. In the first part, the most relevant epidemiological, clinical and therapeutic issues will be discussed. Also, the various available diagnostic methods for imaging rectal cancer, both before and after therapy, will be reviewed. The second part substantiates a personal view on the aforementioned newer techniques, based on four clinical studies. These include the following: a study on the assessment of ADC measurements as a biomarker of tumor aggressiveness; a study of the role of conventional and diffusion-weighted MRI-based volumetry in the assessment of complete response after combined chemoradiation therapy; a study on the assessment of the influence of ROI size and positioning on observer variability and ADC values when measuring ADC of rectal cancers before and after chemoradiation treatment; and a study of the use of perfusion CT for prediction of response to combined chemoradiation therapy.

This thesis represents, above all, the result of combined efforts from a team which generously and voluntarily contributed to its outcome.

As such, gratitude is expressed to Prof. Dr. Filipe Caseiro Alves, Head of Department of the Radiology University Clinic of the University of Coimbra University Hospital and Professor at the Coimbra Medical School. From the outset, his support and scientific contribution were decisive; without him this thesis would not have been possible. His comments, suggestions, and encouragement created the necessary conditions for the work to be developed. I also thank him for his friendship.

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PART I

Chapter I

From pathogenesis to therapy of rectal cancer

1. EPIDEMIOLOGY

1.1. Pathogenesis

The development from a single cellular event to an overt rectal tumor occurs in a stepwise process, involving a progression from normal mucosa to adenoma and then to invasive carcinoma. This development of a malignant lesion occurs through the so-called 'adenoma-carcinoma sequence' [Vogelstein et al, 1988]. In fact, it is now known that the majority of carcinomas develop from benign, pre-neoplastic lesions – adenomatous polyps – following a cascade of changes that take place within the cells of the bowel mucosa. Although the genetic sequence of events occurring in this process is now disclosed, the etiology is multifactorial, involving genetic susceptibility and environmental factors during the initiation and progression of this sequence [ACPGB2I, 2001]. The genetic model for the progression and development of a neoplasm can be represented in a series of genomic events involving alterations in several oncogenes (K-ras) and tumor-suppressor genes (APC, DCC/DPC4, P53), DNA repair genes (hMLH 1 and hMSH2), cell adhesion molecules (epCam), angiogenic factors (VEGF), as well as epigenetic changes (DNA methylation) and microsatellite instability (MSI) [Fisher and Daniels, 2007].

1.2. Incidence

According to the National Oncological Registration ['Registo Oncológico Nacional'] from the year of 2005 (published in 2009), 38519 new cancer cases were diagnosed by the end of that year in Portugal. The overall incidence rate was 284.64/100000.
Among invasive cancers, in locations common to both genders, the most frequent was colorectal cancer (42.76/100000). Specifically rectal cancer by itself ranked as the 7th most common neoplasm in each gender (5.6% and 4.3% of newly diagnosed tumors, respectively in males and females), with 1158 new cases in males and 750 in females. The incidence rate was 22.91/100000 and 13.90/100000 in males and females, respectively, with a global incidence rate for both genders of 18.26/100000.
Over 90% of all rectal tumors corresponded to adenocarcinomas (including the mucinous type).
Age had an impact on rectal cancer incidence greater than any other demographic factor: over 90% of all new cases occurred in patients over 50 years old, with the highest incidence reported for patients older than 75 years old (75.46/100000).
According to previously reported data ['Registo Oncológico Nacional 2001', published in 2008] colorectal cancer was estimated to account for about 10% of the deaths related to cancer in Portugal.

From a worldwide perspective, the incidence and mortality rates for colorectal cancer are greater in developed countries [Parkin et al, 1999; Henderson, 1992]. Nevertheless, in recent times, there is a trend toward a decrease of incidence and mortality rates in some, such as the United States [Jemal et al, 2007]. This modification is attributed to changes in dietary habits and lifestyle factors, as well as to the use of chemoprevention agents. Perhaps the most important factor, however, is a more widespread use of endoscopic methods for screening. In fact, screening for colorectal cancer has been proven to be an effective means of reducing both incidence and mortality from this disease by about 2% and 3% a year, respectively [Nelson et al, 1999].

1.3. Etiology and risk factors

It is now thought that the etiology of colorectal cancer is complex and multifactorial, involving both genetic and environmental factors. These may work in concert to change the mucosa from a premalignant adenomatous polyp to an overt rectal cancer over the course of some years.
Family history yields an increased lifetime risk of colorectal cancer. Familial factors that contribute significantly to increase the risk of sporadic cancer include involvement of at least one first-degree relative (doubling the risk) [Fuchs et al, 1994; Rozen et al, 1987] and appearance of cancer in a close (first or second-degree) relative prior to the age of 60. Furthermore, this increased risk is also established for pre-malignant adenomatous polyps [Pariente et al, 1998; Guillem et al, 1992; Winawer et al, 1996; Ahsan et al, 1998; Kerber et al, 1998].
A dominantly inherited susceptibility to colorectal adenomas and cancer that may account for the majority of sporadic cases of cancer has been suggested [Burt et al, 1985; Ponz de Leon et al, 1992]. Genetic polymorphisms may be of paramount importance in this setting and they may also provide some insights into the geographic variation of this type of cancer as they are known to vary among different ethnic groups [Chen et al, 1998; Potter, 1999].
Regarding familial colorectal cancer, familial adenomatous polyposis (FAP) constitutes 1% of all colorectal cancer incidence. Hundreds of polyps develop in patients in their teen years to the mid-30s and, if the colon and rectum are not surgically removed, 100% of them will end up developing a cancer. There is also an association with extracolonic conditions, both benign (such as mandibular osteomas, supranumerary teeth, desmoid tumors, adrenal adenomas, epidermal cysts and hypertrophy of the retinal pigment epithelium) and malignant (thyroid cancers, duodenal/ampullary carcinomas and brain tumors – the association of brain tumors and colonic polyposis is named Turcot's syndrome) [Rustgi, 1994; Hamilton et al, 1995]. There is an attenuated form of FAP with fewer polyps and a later age of cancer onset in comparison to the classical form [Spirio et al, 1993], related to a mutation of the MYH gene.
Even though FAP is an autosomally dominant condition with almost 100% penetrance, in about 30% of the cases there is a *de novo* mutation without a relevant family history. Patients inherit a mutation on the APC (adenomatosis polyposis coli) gene, and during life they acquire inactivation of the remaining APC gene copy, accelerating the progression to colorectal cancer.
Hereditary non-polyposis colorectal cancer (HNPCC) is responsible for nearly 3% of all colorectal cancers. By opposition to FAP, in this condition there are fewer polyps but there is an accelerated rate of progression to colorectal cancer, with a lifetime risk of about 80% [Marra and Boland, 1996]. HNPCC is an autosomally dominant condition with 80% penetrance. Mutations in one mismatch repair gene result in microsatellite instability, which is responsible for somatic mutations of target genes in HNPCC-related tumors [Chung and Rustgi, 2003].

Hamartomatous polyposis syndromes are rare, representing less than 1% of all colorectal cancers annually. They include Peutz-Jeghers syndrome, juvenile polyposis and Cowden syndrome.

The importance of environmental factors, such as diet and lifestyle, in the genesis of colorectal cancer, is exemplified by the fact that migrants from low-incidence areas to high-incidence areas assume the incidence of the host population in only one generation [Whittemore et al, 1990; McMichael and Giles, 1988] and that economically developed countries have higher incidence and mortality rates [Wilmink, 1997].

Among environmental factors, obesity and high caloric intake were proved to be independent risk factors for colorectal cancer [Slattery et al, 1997; Singh and Fraser, 1998]. Other important risk factors include ingestion of red meat [Wilmink, 1997; Potter, 1999; Slattery et al, 1997; Singh and Fraser, 1998; Willett et al, 1990], as well as consumption of fried, barbecued or processed meat [Chen et al, 1998; Probst-Hensch et al, 1997]. It is however unclear if this carcinogenic effect is due to the high-protein content (that accelerates epithelial proliferation) [Caderni et al, 1999] or to the fatty components of red meat that are metabolized by intestinal bacteria to produce carcinogens (again stimulating epithelial proliferation) [Potter, 1999; Burnstein, 1993]. Furthermore, some authors suggest that saturated animal fats may be especially dangerous [Wilmink, 1997; Potter, 1999].

A sedentary lifestyle may account for an increased risk of developing colorectal cancer, although the exact mechanism remains unknown to date [Wilmink, 1997; Potter, 1999; Whittemore et al, 1990]. Prolonged cigarette smoking is associated also with an increased risk of premalignant adenomas and colorectal cancer [Wilmink, 1997; Potter, 1999; Kikendall et al, 1989]. The associations with the ingestion of coffee, tea and alcohol are still unclear [Seitz et al, 1990; Hartman et al, 1998].

2. CLINICAL AND LABORATORY FINDINGS

The signs and symptoms of rectal cancer do not always point toward a clear diagnosis as there is substantial overlap with some other more frequent proctological conditions such as irritable bowel syndrome, inflammatory bowel disease and especially haemorrhoidal disease. The clinical presentation of rectal cancer is usually with rectal bleeding and a change in bowel habits, which is often an increased frequency of defecation and/or looser stools [Vogelstein et al, 1988]. Rectal bleeding occurs without anal symptoms in over 60% of patients [Ellis et al, 1999; Dodds et al, 1999]. In low rectal cancer, the symptom of tenesmus – the feeling of incomplete evacuation – may occur, and anal pain usually means that invasion of the anal sphincter has occurred [Fisher and Daniels, 2007]. Much less frequently, patients may experience changes in body habits, abdominal pain, weight loss, weakness, anorexia and obstruction [Stein et al, 1993]. A palpable rectal mass is present in 40% to 80% of patients with rectal cancer [Dixon et al, 1990; Finan et al, 1987; Barillari et al, 1996]. If metastatic disease is present, adenopathy, hepatomegaly, jaundice or even pulmonary signs may be apparent. Complications may include acute gastrointestinal bleeding, acute obstruction, perforation and functional impairment of distant organs from metastases.

Laboratory findings may be entirely normal or demonstrate electrolyte derangements, iron-deficiency anemia or abnormalities in liver function tests, as well as an elevation of the carcinoembryonic antigen (CEA) levels. Advances in molecular biological techniques permit extraction of genomic DNA or protein from stool and assay for evidence of genetic alterations

[Villa et al, 1996; Eguchi et al, 1996]. In patients with neoplasms harbouring genetic abnormalities, it is presumed that the stool samples will reveal similar alterations.

3. PRIMARY PREVENTION AND SCREENING

3.1. Primary prevention

The classical belief that a high-fiber diet was protective against the development of colorectal cancer was recently challenged by large, well-controlled studies that failed to prove an inverse relationship between colorectal cancer and fiber intake [Willett et al, 1990; Schatzkin et al, 2000; Alberts et al, 2000]. Nevertheless, a protective effect of vegetables and fruits is thought to be true [Wilmink, 1997; Potter, 1999]. This may be due to the presence of antioxidant vitamins (A, C, E), folate, thioethers, terpenes or plant phenols [Wargovich, 1988].
There is some evidence suggesting that vitamin D may play an important role as an agent for prevention of colorectal cancer. In fact, studies showed that individuals with lower blood vitamin D levels have a higher risk of colorectal cancer and adenoma [Gorham et al, 2007].
The B vitamins – including folate, vitamin B_6 and vitamin B_{12} – may be important for reducing the risk of colorectal cancer. Epidemiologic studies have yielded a link between low-folate intake and a high risk of colorectal cancer [Giovannucci, 2002]. Similarly, recent studies suggested that vitamin B_6 may have a protective effect against colorectal cancer [Larsson et al, 2005].
Calcium, through its mechanism of binding the bile acids with decrease of the intestinal epithelial proliferation, has also historically been assigned as a protective factor against colorectal cancer [Bostick et al, 1995; Potter, 1999]. Observational epidemiologic studies revealed a consistent inverse association between low calcium intake and an increased risk of colorectal cancer [Wu et al, 2002; McCullough et al, 2003].
Population-based studies strongly support a protective role against the appearance of both colorectal adenomas and cancer for aspirin and other non-steroidal anti-inflammatory drugs [Thun et al, 1991; Rosenberg et al, 1998].

3.2. Screening

Screening for rectal cancer usually takes place in the context of the more widespread colorectal cancer screening. It seems well worthwhile to screen for this cancer: it is frequent, and lethal in a large proportion (approximately 50%) of individuals who develop it. Those requisites, however, are not sufficient to warrant a good candidacy for screening: it is mandatory that an effectively curative treatment should be offered for those in whom a diagnosis of early-stage cancer is achieved through screening [Halligan, 2007].
The idea of detecting colorectal cancer early enough to improve survival came from the observation that Dukes' stage A cancers were frequently successfully treated by excision of the tumor [Dukes, 1932]. Since most cancers are believed to begin as adenomas that go additional mutations to become invasive carcinomas (the "adenoma-carcinoma" sequence) and that the malignant transformation is believed to take an average of 10 to 15 years, the removal of polyps has been advocated as a method to prevent colorectal cancer. The relatively slow growth of

adenomatous polyps and cancers, allied to the high incidence rate of these neoplasms, are good reasons warranting an 'aggressive' screening program.
Thus, patients are prevented from ever developing cancer by the screening program and the incidence of the disease is reduced (as opposed to schemes that aim to detect cancer only). Also, the costs of treating (and palliating) cancer are largely eliminated, as is surgery-related morbidity and mortality. Because malignant transformation occurs during the course of many years in the majority of cases, screening can be less frequent than programs that aim to identify overt cancer. Also, screenees who test positive may be less anxious because they are aware that the target lesions (i.e., polyps) are not malignant. However, polyps are smaller and thus more difficult to detect than cancers, and an enormous number of polyps need to be removed to prevent a single cancer [Halligan, 2007].
At least 75% of patients who develop colorectal cancer have no specific risk factors that can be recognized in advance (the most significant risk factor for most individuals is merely age). This means that mass population screening is required in order to impact extensively on the disease. In addition, the large majority of adenomas are destined never to turn into malignancies, but there is essentially no reliable way to distinguish in advance those that will from those that will not. In fact, all detected adenomas can be regarded as potential cancers and should be removed. The larger the adenoma, the more likely it is to become malignant: 1 % at 1 cm or less versus 50% at 2 cm or more [Halligan, 2007].
There is some controversy, however, as to the best approaches and methods to screen patients, since there are several screening methods available.
Cancers tend to bleed and it is this phenomenon on which the rationale for fecal occult blood testing (FOBT) is based. Nevertheless, cancers frequently only bleed intermittently and so multiple testing is needed to enhance sensitivity (conventionally three samples). Even with multiple sampling, sensitivity is just about 40% for cancer. Overall, patients with a repeatedly positive test have a 10% chance of having cancer and a 30%-40% chance of harbouring a large polyp (usually an adenoma 2 cm or larger since these bleed more than smaller ones). Consequently, about 50%-60% of patients with a positive FOBT will have no disease, so FOBT has a relatively low specificity for cancer in those that have tested positive. A major drawback of FOBT is that it is an indirect test – the tumor or polyp itself is not directly seen. Rather, FOBT relies on an epiphenomenon and another test is mandatory to confirm the diagnosis of neoplasia (and to remove it if it is a polyp). However, the majority of adenomas do not bleed and, accordingly, FOBT is poorly suited to a screening program that aims to prevent cancer. In spite all of the problems mentioned above, FOBT is the only screening test for which there are randomized controlled data that demonstrate reduced disease-specific mortality from colorectal cancer when the test is applied to the relevant population. Large-scale trials have shown a decline in disease-specific mortality. Meta–analysis of these trials, performed on data from 329642 screenees, found the reduction in colorectal cancer mortality to be of 23% for those who attended for screening [Towler et al, 1998]. Furthermore, FOBT can be combined in a program with other tests described below.
Newer immunochemical tests that can be used without dietary restrictions, assuring a greater compliance of patients, have been developed [Levin et al, 2003]. They have been studied in case-control studies, and in comparison to the older tests they provide lower rates of false positives and equal or greater sensitivity for polyp detection [Rozen et al, 2000].
Nowadays, research is centred in examining molecular methods in both stool and blood [Ahlquist and Shuber, 2002; Hayes et al, 2005]. Finding the right molecular marker in both approaches is the key to an effective and widespread implementation of these strategies, as large

populations need to be evaluated in order to determine efficacy in comparison to the other screening methods.

Both colonoscopy and flexible sigmoidoscopy are unanimously regarded as viable approaches to screening for colorectal cancer. Contrarily to FOBT, endoscopy is very sensitive for even small adenomas and has a sensitivity for cancer that likely exceeds 95%, mainly because bowel lesions are visualized directly by the operator. Endoscopy is well suited to schemes that aim to detect adenomas and so prevent cancer by polypectomy. However, colonoscopy in particular is expensive, resource-demanding, and difficult to master. Moreover, its potential adverse events such as the risk of perforation are also well recognized, and even the small mortality associated with colonoscopy could theoretically become a true matter of concern in the context of a mass screening program where colonoscopy would be used as the primary screening test [Garvican, 1998]. Other disadvantages of this method include its inherent invasiveness and the need for a thorough bowel cleansing.

Nevertheless, in current US guidelines, colonoscopy is recommended every 10 years in those at average risk. This is based in observational studies, as it is believed that since the average time from development of a polyp to an invasive malignancy is at least 10 years, by screening individuals every 10 years nearly all polyps will be detected before they turn malignant, due to the high sensitivity of the technique [Winawer et al, 2003].

Because of the problems with colonoscopy, it has been suggested that flexible sigmoidoscopy would be a more adequate alternative for screening. Heavy sedation is not required and the left colon is less at risk of perforation during the procedure than the right. It is also less technically demanding than total colonoscopy. Most cancers and adenomas are left-sided and therefore within reach of the sigmoidoscope [Atkin et al, 1993]. Flexible sigmoidoscopy would also determine indirectly those who may be most at risk of right–sided cancer by using left-sided adenomas as a surrogate marker [Garvican, 1998]. Despite the criticisms about the whole colon not being explored, they ignore the particular conditions applying to the screening programs; screenees are asymptomatic and it is fundamental that they come to as little harm as possible as a consequence of the test used [Halligan, 2007].

As such, flexible sigmoidoscopy has replaced rigid proctoscopy/sigmoidoscopy as a method of evaluating the rectum and the sigmoid colon. Several observational studies have estimated a reduction in mortality and incidence of cancers and polyps by screening asymptomatic individuals [Church, 1999].

Barium enema has long been regarded (particularly by radiologists) as an appropriate method for screening for colorectal cancer. It affords the advantages of lack of sedation and hemodynamic monitoring and ability to detect lesions (Figure I.1).

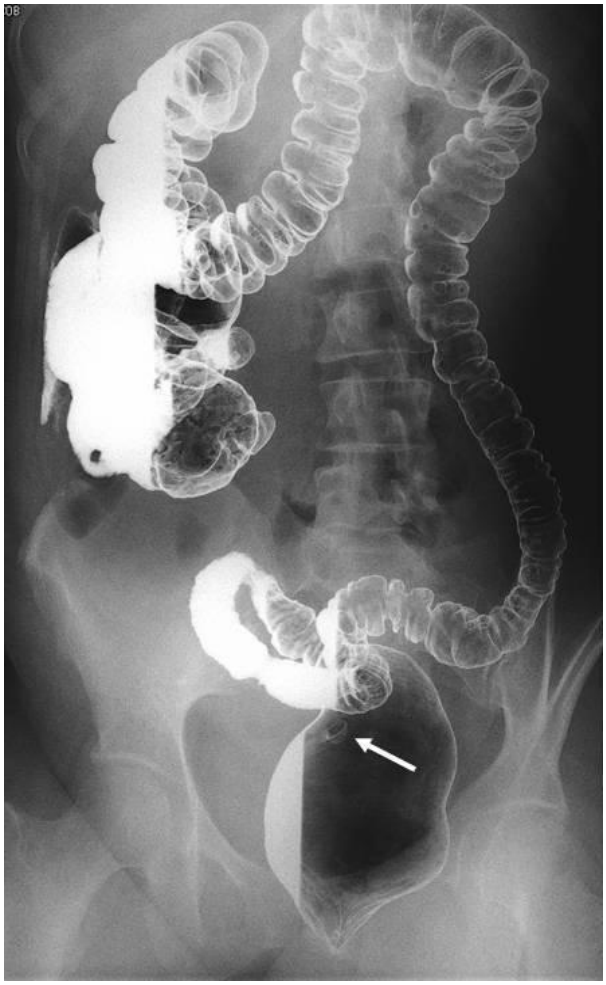


Figure 1.1. Barium enema discloses a rectal polyp with its characteristic 'bowler hat' appearance (white arrow).

It is also relatively cheap and safe. However, we have been witnessing accumulating evidence suggesting that sensitivity for both significant adenomas and early cancers is not high when compared to other methods. For example, the US national polyp study found sensitivity for adenomas 1 cm or larger to be only 48% in 862 paired enema and colonoscopic examinations performed in 580 patients [Winawer et al, 2000]. There are no randomized trials of barium enema that aim to demonstrate an effect on disease-specific mortality from colorectal cancer, and such trials seem unlikely to be performed when there is overwhelming evidence in favour of newer emerging techniques. Therefore, it is uneasy to recognize barium enema playing a major role in a screening program both presently or in the future [Halligan, 2007].

Computed Tomography colonography (CTC), the combination of helical computed tomography (CT) scanning of a cleansed pneumocolorectum with advanced 3D image rendering simulating the colonoscopist's perspective, was first described in 1994 [Vining et al, 1994]. It appears to merge the ideal attributes for a screening test for colorectal cancer – sensitive, specific, safe, and acceptable. It seems widely recognized nowadays that this method can detect polyps with high sensitivity, offering the potential for cancer prevention rather than cure alone. However, debate persists as to with what facility CTC detects polyps overall, with some studies finding it equivalent to optical colonoscopy [Pickhardt et al, 2003] while others have found it no better than barium enema [Rockey et al, 2005]. There have been some attempts to meta-analyze studies of CTC. The most recently published meta-analysed data from 24 studies with 4181 participants [Halligan et al, 2005]. The investigators found a high per-patient average sensitivity of

93% (95% CI: 73% - 98%) and an average specificity of 97% (95% CI: 95% - 99%) for CTC when used to detect polyps 1 cm or larger [Halligan et al, 2005]. Needless to say, test performance decayed when smaller polyps were included in the analysis, with a per-patient average sensitivity of 86% (95%CI: 75% - 93%) and an average specificity of 86% (95%CI: 76% - 93%) when the diagnostic threshold was adjusted to include patients whose polyps were 6 mm or larger. In this meta-analysis, 144 of 150 cancers were detected by CTC, with an overall detection rate of 96% (95%CI: 91% - 99%) [Halligan et al, 2005].

As a screening method, it is of paramount importance that CTC is acceptable to patients. Taylor and colleagues [2005] investigated the experiences of patients having both barium enema and CTC, finding that patients suffered significantly less physical discomfort during CTC and were more satisfied with the procedure overall. Taylor and colleagues [2003a] also investigated the experiences of 186 subjects undergoing CTC followed by flexible sigmoidoscopy or colonoscopy. Again, they found that CTC was significantly less uncomfortable than endoscopy, better tolerated, and was the preferred follow-up investigation of those expressing a preference [Taylor et al, 2003a].

Even if the initial perception was that CTC comprised no risks except for those associated with radiation, this is untrue and this method carries a risk of adverse effects. Burling and colleagues [2006] performed a survey, gathering data on 17067 procedures from 50 United Kingdom centres: 13 patients (0.08%) suffered a potentially serious adverse event attributable to CTC, 9 of which were perforations. Four of them were asymptomatic, yielding a symptomatic perforation rate of 0.03% (1 in 3413 patients) versus 0.13% for optical colonoscopy [Burling et al, 2006]. The same group investigated the degree of cardiovascular compromise experienced by patients undergoing both CTC and colonoscopy, since it is believed that cardiovascular depression as a consequence of sedation is a significant cause of serious adverse events during colonoscopy [Taylor et al, 2003b]. CTC was associated only with a mild tachycardia related to administration of intravenous spasmolytics whereas colonoscopy was associated with potentially serious cardiac arrhythmias and cardiovascular depression.

Computer-assisted detection (CAD) systems have recently become widely available in the commercial marketplace. They accelerate interpretation, making it more time-efficient and less tedious [Bond, 2005]. The largest study to evaluate its performance in isolation – i.e., the CAD algorithm is applied to CTC studies where the location of polyps is known – was performed by Summers and colleagues who found that CAD detected 89.3% of polyps 10 mm or larger in a test set of 792 patients [Summers et al, 2005]. The potential benefit of CAD assistance has been inferred indirectly by comparing the sensitivity of CAD and radiologists when asked to interpret the same dataset: Taylor and co-workers found that CAD was more sensitive than any of three experienced observers [Taylor et al, 2006]. Also, interpretation time decreased significantly; by a mean of 1.9 minutes per patient for those with polyps and by 2.9 minutes for those without [Halligan et al, 2006].

There is no proof whatsoever that CTC is able to reduce disease-specific mortality in the context of screening for colorectal cancer. However, case-control studies provided indirect evidence that polypectomy reduces the incidence of subsequent cancer [Atkin et al, 1992; Selby et al, 1992]. It is on this type of study that the success of CTC is predicated; if polypectomy reduces cancer, and CTC is good at detecting polyps, then it must follow that it can prevent cancer [Halligan, 2007].

4. STAGING AND PROGNOSIS

Standard clinical-pathological staging is the best indicator of prognosis for patients with rectal cancer and nowadays they have both a clinical presurgical staging, as well as a postoperative surgical stage. Since a significant proportion of patients (10% to 30%) experience a substantial downstaging with disappearance of the primary tumor (pathological complete response) presurgical clinical staging should be still the cornerstone for decisions on the administration of neoadjuvant therapy and on the surgical procedure of choice. As such, we are presently witnessing a growing need for the initial staging to be as accurate as possible, as it impacts significantly on both management and prognosis of patients.

The routine non-imaging staging procedures include a clinical history, a physical examination, blood cell count, liver and kidney function tests and a CEA level determination. A thorough physical examination is an essential part of the pretherapeutic evaluation in order to assess the distance of the tumor from the anal verge or the dentate line, involvement of the anal sphincter, amount of circumferential involvement, clinical fixation and sphincter tone. So far the digital examination has not been replaced by any endoscopic or imaging methods in this regard.

The imaging techniques for staging rectal cancer will be discussed further ahead, in Chapter II.

The Dukes classification [Dukes, 1932] was used for many years but it should now be regarded as of historical significance only and discarded for clinical use.

Staging is now performed according to the tumor-node-metastasis (TNM) classification of the American Joint Commission on Cancer (AJCC) / Union Internationale Contre le Cancer (UICC) staging system [Edge et al, 2010].

The TNM staging system classifies the extent of cancer based on anatomical information about the size and extent of primary tumor (T), the regional lymph node status (N) and the distant metastases (M), grouping the cases with similar prognostic. The 7th revision of TNM staging was recently published by the AJCC and UICC, and became operational starting from 2010.01.01 [Edge et al, 2010].

Research studies during the last years yielded a much better understanding of carcinogenesis and emphasized the significant role of an increasing number of non-anatomic markers in establishing the prognosis and treatment response of the neoplastic patient. This led to the recognition that staging based only on anatomical features no longer provides an adequate answer to the recent advances in clinical evaluation and therapeutic decisions.

The 7th revision of TNM staging was designed to respond to these needs, including – in comparison with the previous editions – more markers which were fully validated as being relevant in clinical practice for accurate therapeutic decision making [Edge et al, 2010].

Despite that, by recognizing the fact that anatomical data still possess a crucial prognostic role, the actual TNM system maintains a division between the anatomic and non-anatomic factors. Therefore, the anatomic extent of the neoplastic disease remains the nucleus of the staging for two reasons: (1) to keep a reporting format which is compatible with previous versions, in order to allow comparability of the prognosis of present patients (treated according to new prognostic markers, including non-anatomic ones) vs. patients who have been staged according to previous versions, and (2) the inclusion of new prognostic factors is limited both by their validation only for discrete subsets of patients and by the achieved level of evidence, which is still unsatisfactory at the light of the current knowledge. The accepted non-anatomic factors were considered to be significant, thus being included in a separate section in the staging form. Clinical (*c*) and pathologic (*p*) stages can be complementary for a complete staging [Edge et al, 2010].

According to the 7th edition of the AJCC/UICC TNM staging, the descriptions of the several stages for each parameter are the following:

- *Primary Tumor (T)*

TX - Primary tumor cannot be assessed

T0 - No evidence of primary tumor

Tis - Carcinoma in situ: intraepithelial or invasion of lamina propria

T1 - Tumor invades submucosa

T2 - Tumor invades muscularis propria

T3 - Tumor invades through the muscularis propria into pericolorectal tissues

T4a - Tumor penetrates to the surface of the visceral peritoneum

T4b - Tumor directly invades or is adherent to other organs or structures

- *Regional Lymph Nodes (N)*

NX - Regional lymph nodes cannot be assessed

N0 - No regional lymph node metastasis

N1 - Metastasis in 1–3 regional lymph nodes

N1a - Metastasis in 1 regional lymph node

N1b - Metastasis in 2–3 regional lymph nodes

N1c - Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized perirectal tissues without regional nodal metastasis

N2 - Metastasis in 4 or more regional lymph nodes

N2a - Metastasis in 4–6 regional lymph nodes

N2b - Metastasis in 7 or more regional lymph nodes

- *Distant Metastasis (M)*

M0 - No distant metastasis

M1 - Distant metastasis

M1a - Metastasis confined to one organ or site (for example, liver, lung, ovary, non-regional node)

M1b - Metastases in more than one organ/site or the peritoneum

By AJCC/UICC convention, the designation "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. Clinical classification (cTNM) is usually performed before treatment during an initial evaluation of the patient or when pathologic classification is not possible. For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y" and "r" prefixes are used. Although they do not directly affect the stage grouping, they indicate cases needing separate analysis. The "m" suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses:

pT(m)NM. The "y" prefix indicates those cases in which classification is carried out during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the "r" prefix: rTNM [Edge et al, 2010].
Patients are then grouped according to the following anatomic stage/prognostic groups:

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T4a	N0	M0
Stage II C	T4b	N0	M0
Stage III A	T1-T2	N1	M0
	T1	N2a	M0
Stage III B	T3-T4a	N1	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage III C	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IV A	Any T	Any N	M1a
Stage IV B	Any T	Any N	M1b

The 7th edition of the TNM staging shows some changes in comparison with the previous version, which include the following [Obrocea et al, 2011]:

- T4 category has been subdivided into T4a (tumor penetrates to the surface of the visceral peritoneum) and T4b (tumor directly invades or is adherent to other organs and structures).
- The recommendation of 6th edition to harvest at least 12 to 14 regional lymph nodes [Goldstein and Turner, 2000; Puppa et al, 2007; Chang et al, 2007; Greene et al, 2006; Rigby et al, 1999] is rephrased. It is emphasized the importance of mentioning in the pathological report the total number of nodes evaluated, since data from recent years suggest the prognostic significance of this issue [Chang et al, 2007].
- pN1 – metastasis in 1 to 3 regional lymph nodes – has been subdivided in N1a (metastasis in 1 regional lymph node), N1b (metastasis in 2–3 regional lymph nodes) and N1c (tumor deposits in the perirectal tissue without regional lymph node metastasis). Tumor deposits (TD, formerly named satellite nodules) are included both in *Site-Specific Factors* (or *Prognostic Factors*) category and also in the N category. They have been described in recent studies as an independent prognostic factor [Goldstein and Turner, 2000; Puppa et al, 2007] and are defined as discrete foci of tumor lying in the perirectal

fat, in the absence of residual lymph node tissue, but within the lymphatic drainage area of the primary tumor. The TD's should be mentioned (by number) in the *Site-Specific Prognostic Factors* section and also in the N1c category in case of T1 or T2 stage lesions.

- pN2 – metastasis in 4 or more regional lymph nodes – has been subdivided in pN2a – metastasis in 4 to 6 regional lymph nodes – and pN2b – metastasis in 7 or more nodes.
- M – MX is no longer included in the 7th edition of the TNM system. The M0 category cannot be documented on pathological evaluation, but only clinical, based on the clinical history and physical examination. M1 has been subdivided in M1a (metastasis confined to one organ or site) and M1b (metastasis in more than one organ/site or the peritoneum).
- Stage II – is now subdivided in II A (T3N0), II B (T4aN0) and II C (T4bN0).
- Stage III – T4bN1, previously classified as III B, has been reclassified as III C. For the same reasons (different survival rates), a number of N2 categories (formerly included in stage III C) have been restaged as follows: T1N2a in stage III A and T1N2b, T2N2a-b and T3N2a in stage III B.

Meanwhile, seven new prognostic factors have been incorporated. Even though none of them is considered mandatory for staging in the present classification, their prognostic and predictive value has been acknowledged, making them extremely helpful for a personalized diagnosis and targeted therapy, in light of recent research [Obrocea et al, 2011; Edge et al, 2010]:

- *Tumor deposits*, mentioned above, are recorded numerically.
- For *circumferential resection margin* (CRM), the distance in mm from the closest tumor margin to the mesorectal fascia (MRF) must be reported. A margin <1 mm is considered to be positive (invaded by tumor) [Edge et al, 2010].
- *Perineural invasion* (PN) – presence or absence of PN must be mentioned.
- *Microsatellite instability* – sporadic cancers which are microsatellite unstable (MSI-H phenotype) have a better prognostic than tumors with similar anatomic stage and histological grade but without MSI-H phenotype. The MSI status must be reported as follows: stable, MSI-low, MSI-high and not registered.
- *Tumor regression grade (TRG)* – should be interpreted as a marker of response to neoadjuvant therapy. A 4-grade system is recommended [Edge et al, 2010]:
    - Grade 0 (complete response) – no viable cells present;
    - Grade 1 (moderate response) – single cells or small groups of cancer cells;
    - Grade 2 (minimal response) – residual cancer outgrown by fibrosis;
    - Grade 3 (poor response) – minimal or no tumor kill, extensive residual cancer.
- *k-ras gene analysis* – mutation of k-ras gene is associated with an unfavorable response to treatment with anti-EGFR antibodies.
- *18q loss of heterozygoity (LOH) assay* – is considered currently a prognostic marker; based on 18qLOH assay it could be possible to decide which stage II patients should receive neoadjuvant treatment.

The L (lymphatic vessel invasion) and V (venous invasion) discriminators have now been merged into lymph-vascular invasion (LV), together with a new subdivision: LV not present (absent/not identified), LV present/identified, not applicable and unknown/indeterminate.

The R category (residual tumor) has been reconfigured as follows: RX – presence of residual tumor cannot be assessed, R0 – no residual tumor, R1 – microscopic residual tumor, and R2 – macroscopic residual tumor.

These prognostic features are able to differentiate outcomes of rectal tumors. The involvement of the MRF was identified as a poor prognostic marker two decades ago. A recent meta-analysis of studies, including 17,000 patients by Nagtegaal and Quirke [2008] showed that a positive

CRM strongly predicts for local recurrence, especially in patients who have received neoadjuvant CRT (hazard ratio [HR] = 6.3) but also distant metastases (HR = 2.8) and poor survival (HR for survival = 1.7). Other prognosticators that influence outcomes include for example the presence of extramural venous invasion (3-year relapse-free survival, 35% vs. 74.1%, $P < 0.001$) [Smith et al, 2008a,b], extramural spread beyond 5 mm (5-year disease-specific survival, 54.1% vs. 85.4%, $P < 0.0001$) [Merkel et al, 2001; MERCURY Study Group, 2007], increased nodal stage (5-year overall survival [OS] by stage: T3N0, 64% vs. T3N1, 52.4% vs. T3N2, 37.5%) [Gunderson et al, 2010] and a low rectal tumor requiring abdominoperineal resection (5-year cancer-specific survival 65.1% for APR vs. 76.6% for low anterior resection, $P < 0.001$) [Hawkes et al, 2011]. These features highlight the need for careful staging and individualized management based on prognostic factors.

5. TREATMENT OPTIONS

The universal implementation of total mesorectal excision (TME) and neoadjuvant (short-course) radiotherapy (SCRT) or long-course combined chemoradiation therapy (CRT) have reduced local recurrence rates from 25% - 40% to under 10% [Heald et al, 1998; Kapiteijn et al, 2001; Havenga et al, 1999; Nesbakken et al, 2002].

5.1. Surgery

It is generally considered that the surgical management of primary rectal cancer may present particular problems to surgeons due in part to anatomic constraints of the pelvis and also to the complex anatomy of the region.

For selected superficial lesions without evidence of nodal disease, transanal local excision often provides adequate resection of the primary tumor mass and can avoid a more extensive resection, sparing the patient to considerable morbidity, and has long been used as an alternative surgical option for patients not fit to undergo a major abdominal resection or unwilling to have a permanent stoma. According to several authors [Winde et al, 1996; Sengupta and Tjandra, 2001; Blair and Ellenhorn, 2000], local excision may be curative for patients with a primary tumor limited to the mucosa. Even if the tumor invades the submucosa, local excision may be potentially curative as long as high-risk features, which increase the likelihood of local and regional nodal metastatic disease, are not present. As such, tumors should be within 8 to 10 cm of the anal verge, encompass less than 40% of the bowel wall circumference, show no ulceration, have a well or moderately-well differentiated non-mucinous histology and show absence of pathological evidence of venous or lymphangiovascular invasion on biopsy. The benefits of local excision for these patients are preservation of anal continence as well as bladder and sexual functions, with identical oncologic results [Lezoche et al, 2005; Winde et al, 1996; Sengupta and Tjandra, 2001; Blair and Ellenhorn, 2000].

Even if rectal tumors limited to the submucosa (T1) are reported to be at low risk for local recurrence and may therefore be eligible for local excision, once the tumor invades the muscularis propria (T2), the available evidence [Lezoche et al, 2005; Varma et al, 1999; Balch et al, 2006; Rodel et al, 2005; Martling et al, 2000, Marijnen and Glimelius, 2002] shows that local excision alone may be associated with high local recurrence rates. In fact, success of local excision in the management of rectal cancer depends on the depth of tumor invasion, and this is

correlated with the risk of lymph node metastases [Bozzetto et al, 1999]. Accurate preoperative assessment of the level of invasion is important because the risk of lymph node metastases increases with T stage. The risk is 0%–12% for T1, 12%–28% for T2, and 36%–79% for T3–T4 lesions [Varma et al, 1999].

Performing a good transanal excision requires substantial expertise as the surgeon must retain control over the primary tumor and obtain adequate mucosal margins as well as adequate deep resection into perirectal fat. The staging of such lesions should be performed using endorectal ultrasound (EUS) to minimize the likelihood of performing a local excision for T3 tumors [Herzog et al, 1993].

The primary treatment of patients with stages II and III rectal cancer (T3/4 and/or N positive) is surgical. However, contrarily to patients with stage I cancers, it is now widely accepted that combined modality therapy with radiation therapy (RT) with or without chemotherapy should be used in conjunction with surgery. Surgery should aim at the preservation of intestinal continuity and sphincter mechanism, and at the same time should maximize tumor control. Lesions in the upper third of the rectum are usually managed with a low anterior resection in much the same way as a sigmoid cancer. An adequate distal margin can be obtained for these lesions way above the sphincteric complex [Colquhoun and Wexner, 2002].

Lesions in the two distal thirds lie below the peritoneal reflection and are usually more difficult to manage surgically. This is related to the confines of the pelvic bones and also to the fact that depending on the size and location of the neoplasm, the sphincteric complex may be invaded and an adequate distal margin may not be achievable. Despite this, tumors of the middle third can usually be resected safely with a low anterior resection. For neoplasms of the distal third of the rectum, the surgical excision could be particularly challenging. Here the main concern is sphincter preservation, which is influenced by the extent of invasion of the lesion into the muscles of the sphincteric complex and also by the distance between the distal end of the lesion and the musculature of the anal canal. For these tumors, the classical surgical approach consisted of an APR. This type of resection, despite its association with a relatively low local recurrence rate, implicates a permanent colostomy with loss of the intestinal continuity and of the sphincteric function.

In order to increase the number or sphincter-preserving operations performed, several authors cite the use of preoperative CRT as a mean to decrease the local recurrence rate [Ota et al, 2002]. Such an approach would be able to reduce the need for APR to an incidence of 10% or less. When performing a sphincter-preserving operation, in order to preserve the lateral musculature and therefore a functional sphincter complex, the resection by necessity does not have a margin as wide as one performed during an APR. In order to improve the margin status, intersphincteric resections have been performed [Tiret et al, 2003]. This approach includes a partial sphincteric resection designed to improve margin status without sacrificing sphincter function. In small series, functional results have been comparable to less aggressive sphincter-preserving operations. The impact on oncologic outcome is difficult to interpret and will require larger series.

Not infrequently, large rectal tumors invade through the wall of the rectum and the mesorectal fat into contiguous structures. However, carefully selected patients with locally advanced or recurrent rectal cancers may benefit from an aggressive approach such as a total pelvic exenteration, since most recurrences remain limited to the pelvis [Mukherjee, 1999].

Despite a strong debate about the impact of total pelvic exenteration over survival, its potential benefits on controlling loco-regional disease and preventing significant morbidity from

recurrence (including pain, tenesmus, obstruction and fistula) keep this technique as an important tool in the surgical approach of large rectal tumors.

5.1.1. Total Mesorectal Excision

The goal of the resection of rectal cancer is to eradicate the neoplasm with an adequate margin and at the same time to resect the draining lymph nodes and lymphatics in order to satisfactorily stage the tumor and to decrease the risk of local recurrence and spread.
During the later part of the past century, refinements of the surgical technique led to an improvement in survival, principally through a reduction in surgical morbidity; but the major problem facing surgeons who performed rectal resection was the subsequent development of local recurrence within the pelvis. When present, there was a 5-year survival lower than 5%. In fact, the series reported from 1940 to 1980 in the surgical literature report local recurrence rates from 10% to 49% [Philips et al, 1984; Pescatori et al, 1987]. The identification that the cause of local recurrence was the incomplete removal of the rectum and its draining lymphatics contained within the mesorectum was the key determinant in improving surgical outcome [Heald et al, 1982]. This, in parallel with the recognition of the pathologically assessed CRM, which have been shown to be more important than the distal mucosal margins with respect to the risk of local recurrence [Kuvshinoff et al, 2001; Willett, 2000], led to the dramatic fall in local recurrence rates that have been seen following the acceptance of the principle of TME [Heald et al, 1998]. The key feature of this surgical principle is the identification of the plane of cleavage along which surgical resection must be performed. This has become recognized as the "Holy Plane" (of Heald) [Heald, 1988]. The theory behind TME is that cancer spread will tend, at least initially, to remain within the embryological hindgut "envelope" – the mesorectum. The bowel remains separate from the other organs by a collagenous areolar tissue that surgically forms a "plane that can be cleaved at operation" and is almost entirely avascular. In performing a TME, it is the dissection along this perimesorectal avascular plane around the midline hindgut into the depths of the pelvis that led to an improvement in local recurrence rates [Heald, 1988]. This procedure has reduced local recurrence rates in rectal cancer from 39% to 10% and increased 5-year-survival rates to 71% [Köckerling et al, 1998], becoming one of the most influential factors in rectal cancer outcomes and considered nowadays the standard of care for surgical practice [Nelson et al, 2001]. Moreover, Leite et al [2011] demonstrated that the outcome of surgical treatment of rectal cancer is related to the completeness of mesorectal excision, which is a more discriminative prognostic factor than the classic tumour-node-metastasis (TNM) system.
The radiologist has an important role in providing the surgeon relevant information about the tumor location within the rectum, its depth of spread within the mesorectum, its relationship to the MRF, the surrounding organs and to the anal sphincter, and the presence of other adverse factors, such as involved lymph nodes or vessels. These data will further allow significant improvements in the planning of the surgery.
The surgical consequences of TME may include erectile or bladder impairment due to disruption of sympathetic or parasympathetic nerves located in proximity of the mesorectum. Therefore, the procedure should be performed by an experienced surgeon in order to minimize morbidity [Mancini et al, 2000]. Several authors have now demonstrated the feasibility of laparoscopic TME in a safe manner [Zhou et al, 2003; Tsang et al, 2003; Morino et al, 2003], but there is no

adequate follow-up yet that can demonstrate whether there are oncologic advantages to such an approach.

5.2. Neoadjuvant therapy

Since the 5-year survival rates now are greater than 90% in stage T1-T2, N0 tumors, the addition of neoadjuvant treatment to surgery is usually reserved for patients with operable T3-4, N0-2 neoplasms as determined by imaging methods [Hawkes et al, 2011].
The advantages of such a pre-operative treatment strategy are pertinent and include the following: allowing downstaging of the primary tumor, thus increasing the likelihood of an R0 resection and/or sphincter-preserving surgery; improving tumoral radiosensitivity by delivering radiation to better oxygenated tissues; offering early relief from tumor-related symptoms; and decreasing acute and chronic toxicity rates in comparison with postoperative CRT.
A number of treatment regimens have been given to patients with rectal cancer. The most commonly used consist of RT (with or without combined chemotherapy) and chemotherapy.

5.2.1. Radiation Therapy

In Europe several large trials have evaluated a short preoperative course of RT followed by immediate surgery, indicating an important benefit of this regimen over surgery alone [Kapiteijn et al, 2001; Sebag-Montefiore et al, 2009; Swedish Rectal Cancer Trial, 1997].
The advantages of neoadjuvant RT are thought to be due to improved responsiveness of tissue which has not already been rendered hypoxic by previous surgery. In theory, ionizing radiation is more effective in the irradiation of virgin tissue due to the increased oxygen tension in it [Julien and Thorson, 2010].
As a result, such a short course of preoperative RT has now become standard in many European institutions for some patients with rectal cancer. The SCRT protocol consists of a daily dose of 5 Gy delivered during 5 days (to a total of 25 Gy) with surgery carried out during the following 5–10 days [Julien and Thorson, 2010]. Nevertheless, this short course is insufficient for the more advanced tumors where downsizing is required, and these patients are normally submitted to a long course of combined CRT pre-operatively [Beets-Tan and Beets, 2011].
Neoadjuvant RT for rectal cancer was studied quite extensively. Initial randomized studies compared neoadjuvant RT followed by surgery to surgical therapy alone in order to determine whether there was a difference in the outcome of patients. Two landmark studies performed during this period included the Swedish Rectal Cancer Trial [Swedish Rectal Cancer Trial, 1997] and the Dutch Rectal Cancer Study Group [Kapiteijn et al, 2001]. Both demonstrated a decline in the local recurrence rates in the preoperative RT plus surgery groups in comparison to the surgery alone groups. In the Swedish Rectal Cancer Trial [1997] the local recurrence rate after 5 years was 11% in the group receiving RT prior to surgery and 27% in the group treated with surgery alone ($P < 0.001$). The 5-year overall survival rate was 58% in the RT plus surgery group compared to 48% in the surgery-alone group ($P < 0.004$) [Swedish Rectal Cancer Trial, 1997]. The Dutch Rectal Cancer Study Group found a local recurrence rate of 2.4% in the RT plus surgery group and a rate of 8.2% in the surgery-only group ($P<0.001$) [Kapiteijn et al, 2001]. However, unlike the Swedish Trial, this study did not confirm a difference in the overall survival of both groups. Despite these discrepancies in overall survival, the data from both studies

consistently demonstrated that neoadjuvant RT is able to afford a significant reduction in local recurrence rates for stage II and III rectal cancers.

Heterogeneous results have been found in over 20 randomized controlled trials (RCTs) comparing preoperative RT and surgery to surgical therapy alone. Three meta-analyses which have been conducted to better understand inconsistencies between these trials [Colorectal Cancer Collaborative Group, 2001; Figueredo et al, 2003; Cammà et al, 2000], concurred in the demonstration of a significant reduction in the local recurrence rate of stage II and III rectal cancers treated with RT prior to resection, whereas only two of the three studies found an improvement in overall survival. The meta-analysis by Cammà et al [2000] evaluated 14 RCTs to report a significant reduction in 5-year-overall-mortality rates, cancer-related mortality rates, and local recurrence rates. Another meta-analysis conducted by the Colorectal Cancer Collaborative Group [2001] analysed 22 RCTs comparing preoperative, postoperative, or no RT in rectal cancer. This study concluded that preoperative RT, at doses of 30 Gy, reduces the risk of local recurrence and death from rectal cancer. A third meta-analysis of RCTs by Figueredo et al. [2003] found local recurrence rates to be lower with preoperative RT but also concluded that a benefit on survival is achieved when postoperative chemotherapy is used in combination to preoperative RT.

In summary, there is a clear association of pelvic RT with decreased local recurrence and a high, but somewhat lesser likelihood of improved survival.

Despite these important benefits, the toxicity of pelvic RT for rectal cancer can be problematical. Although acute side effects and surgical complications are only marginally increased with the addition of preoperative RT to surgery [Marijnen et al, 2005], the impact of neoadjuvant SCRT on long-term toxicities has been established in large randomized trials. In the Dutch Colorectal Cancer Group study, irradiated patients experienced significantly higher rates of fecal incontinence (62% vs 38%, $P < 0.001$), including the need for incontinence pads, anal blood loss (11% vs 3%, $P < 0.004$) and mucous loss (27% vs 15%, $P < 0.005$), and increased bowel frequency when compared with those who underwent TME alone [Peeters et al, 2005]. The long-term follow-up from the Swedish Rectal Cancer Trial reported higher hospital admission rates in irradiated patients within the first 6 months (relative risk = 1.64; 95% confidence interval [CI], 1.21-2.22). No difference was seen in late admissions overall, but irradiated patients had an increased likelihood of being admitted for bowel obstruction ($P = 0.02$), abdominal pain ($P = 0.01$), and nausea ($P = 0.03$) as late sequelae [Birgisson et al, 2005]. Sexual dysfunction is also a major issue as shown by the same Dutch group that evaluated 990 patients for quality of life and sexual function. The most notable deterioration was in the irradiated group in terms of sexual activity (males, $P = 0.06$; females, $P = 0.01$), and both erectile and ejaculatory problems were higher in irradiated males ($P = 0.02$) [Marijnen et al, 2005]. One should remember that these trials evaluated SCRT, which is generally given to patients with better prognosis tumors at a lower risk of recurrence, and, therefore, in whom the acceptability of late sequelae is lower. However, RT techniques are evolving rapidly, and there is the potential for more focused delivery, with increased sparing of normal tissue and reduced toxicity [Hawkes et al, 2011].

5.2.2. Combined Chemoradiation Therapy

The clinical advantages of RT in locally advanced rectal cancer, combined with the evidence that adjuvant chemotherapy also improves survival, provided a solid rationale to study the combination of these therapies [Julien and Thorson, 2010]. Following a consensus statement of

the National Institutes of Health (NIH) in 1990, postoperative combined CRT became the standard of care for stage II–III rectal cancer in the US and many other countries [NIH Consensus Conference, 1990]. However, in 2004 a trial convincingly showed that CRT is better administered preoperatively than postoperatively (as it is more effective in producing tumor necrosis in the non-disturbed presurgical tumor bed and cancer cells of the tumor periphery compared to the hypoxic postsurgical bed), a fact that gave rise to a gradual change in practice [Sauer et al, 2004]. The combination of neoadjuvant chemotherapy and RT is now considered the standard of care in the treatment of locally advanced rectal cancer.

Long-course CRT uses conventional fractionated RT (45–50 Gy) divided into 1.8 or 2.0 Gy over 25–33 days concurrently with chemotherapy. Patients typically undergo surgery 4 to 8 weeks after CRT is given.

The German Rectal Cancer Study Group [Sauer et al,2004] evaluated stage II and III rectal cancer treated with a combination of preoperative chemotherapy, RT, and TME versus TME combined with postoperative CRT. Preoperative therapy consisted of 50 Gy over 5 weeks with 120-hr continuous intravenous infusion of 5-fluorouracil (5-FU) per day during the first and fifth weeks of RT. TME was performed 6 weeks after treatment. The chemotherapy and RT was identical in the postoperative group, except for the delivery of a 540 cGy boost to the tumor bed. No difference in 5-year survival rates were found between these two groups (76% and 74%, $P = 0.80$) [Sauer et al, 2004]. The study did find, however, a significant decrease in local recurrence rate in the preoperative treatment arm compared to the arm receiving CRT in the postoperative period (6% vs. 13%) ($P = 0.006$) [Sauer et al, 2004]. Findings in the group receiving preoperative CRT also included evidence of improved tumor downstaging, appreciated as earlier TNM stages ($P < 0.001$) and, obviously, more pathologic complete response (pCR) rates (8% vs. 0%) ($P < 0.001$) [Sauer et al, 2004]. Other noteworthy results included the analogous rates of sphincter preservation and morbidity and mortality between these groups despite a superior number of distal tumors in the preoperative group (39 vs. 30 at <5 cm; $P = 0.008$) [Sauer et al, 2004]. The study also found an improved treatment compliance in the preoperative group (92% vs. 50%) along with less acute serious toxic side effects ($P = 0.001$) and long-term toxic effects ($P = 0.01$) in the preoperative treatment group (27% vs. 40%) [Sauer et al, 2004]. These results clearly show that, although the primary outcome of overall survival was not different among these groups, there are a number of advantages of preoperative CRT over therapy given in the postoperative period in stage II and III rectal cancer.

A more recent clinical trial found similar results in the assessment of preoperative CRT in patients with locally advanced rectal cancer. The Fédération Francophone de Cancérologie Digestive (FFCD) 9203 trial [Gérard et al, 2006] enrolled 733 patients with resectable T3 or T4, Nx, M0 rectal adenocarcinoma. Patients were randomly assigned to preoperative RT alone (45 Gy in 25 fractions over 5 weeks), or preoperative RT (same protocol) plus concurrent chemotherapy, consisting of 5-FU and leucovorin during the first and fifth weeks of treatment. Neoadjuvant CRT resulted in increased pCR rates (11.4% vs. 3.6%, $P < 0.05$) and decreased rates of local recurrence (8.1% vs. 16.5%, $P < 0.05$) [Gérard et al, 2006]. However, this trial similarly did not find a difference in 5-year-survival rates between the two arms of the study.

Similarly, multiple randomized trials have been unable to show a survival benefit with CRT compared to RT alone. Despite this, lower local recurrence rates with the addition of chemotherapy are consistently found. Furthermore, secondary outcomes in these trials have provided even more evidence of the advantages in using CRT in the preoperative setting as opposed to providing it postoperatively: improved rates of tumor downstaging, significantly

higher pCR rates, and enhanced treatment compliance rates in groups who received CRT before surgery [Bosset et al, 2006; Gérard et al, 2006; Sauer et al, 2004].
Tumor downstaging has been reported to occur in approximately 60% of patients who undergo preoperative RT with concurrent continuous intravenous infusion 5-FU [Garcia-Aguilar et al, 2003]. After mesorectal excision, the pCR rates are reported to be comprised between 10% and 30% [Janjan et al, 1999; Brown et al, 2003].

5.2.3. Chemotherapy

Despite the efficacy of postoperative chemotherapy, only 40% to 60% is administered at full dose, most commonly because of toxicity [Bosset et al, 2006; Rodel et al, 2007; Sauer et al, 2004]. Thus, several phase II studies have incorporated chemotherapy into the preoperative management of high-risk patients.
In a single-arm phase II study, Chau et al [2003] administered 12 weeks of 5-FU plus mitomycin C before CRT and postoperatively to 36 patients with locally advanced tumors (at least T3 disease on digital rectal examination and imaging). The overall response rate to neoadjuvant chemotherapy was 27.8%, increasing to 81% after CRT, with 65% of patients experiencing improved symptoms during neoadjuvant chemotherapy. R0 resections were achieved in 28 of 34 patients. Treatment was well tolerated, with 61% completing postoperative chemotherapy.
The larger EXPERT trial [Chua et al, 2010] enrolled 105 eligible poor-risk patients (defined as at least one of CRM-positive, T3 low-lying tumor at or below the levators, extension >5 mm into perirectal fat, T4N0-2 or T1-4N2 tumor) to a similar design, replacing 5-FU and mitomycin C with capecitabine and oxaliplatin (CAPOX). Results showed considerably higher radiologic response rates with the neoadjuvant chemotherapy (74%) and CRT (89%). Ninety-three of 97 patients had R0 resections with 21 patients achieving a pCR with evidence of downstaging in 76% of tumors. Seventy-eight of the 97 patients (80%) who underwent surgery completed postoperative chemotherapy. Eleven patients (10%) did not complete neoadjuvant chemotherapy because of toxicity, whereas 19% were unable to receive any adjuvant chemotherapy, mainly because of postoperative complications.
The Grupo Cancer de Recto 3 study [Fernández-Martos et al, 2010] randomized 108 patients to receive induction CAPOX or adjuvant CAPOX in combination with CRT and surgery and reported that R0 resection, pCR, and tumor downstaging rates were similar in both arms. Tumor downstaging was lower than reported in the EXPERT study (58% in the induction arm vs. 89% in the EXPERT study); however, this study incorporated a lower ratio of cT4 or CRM-involved tumors than previous studies, and the RT dose was also slightly lower (50.4 vs 54 Gy). Nonetheless, these results still provide a strong argument for induction chemotherapy based on the toxicity profile. Only 2% of patients in the induction arm were unable to complete study treatment because of adverse events compared with 17% in the adjuvant arm, whereas rates of serious toxic effects were significantly more common in the adjuvant arm (19% induction arm vs. 54% adjuvant arm, $P = 0.0004$).
From these trials, it appears that the delivery of neoadjuvant chemotherapy is better tolerated than adjuvant treatment and may offer benefit over CRT alone; however, this approach needs evaluation in a phase III randomized controlled setting.
Rationale for neoadjuvant chemotherapy without CRT includes the ability to begin anti-tumor therapy immediately, rather than delaying systemic therapy to administer local strategies and better surgical outcomes because of tumor downstaging. Omitting CRT would avoid important

RT-associated toxicities, such as infertility and loss of sexual function, preoperative fibrosis, and tissue friability. Chemotherapy also provides an opportunity for the early recognition of patients who will not benefit from standard protocols and may necessitate intensified regimens. The EXPERT trial showed promising downstaging and symptom improvement after CAPOX chemotherapy [Chua et al, 2010], suggesting that further evaluation of neoadjuvant chemotherapy alone is warranted.

Serious long-term toxicity from chemotherapy is infrequent. There is a theoretical risk of secondary malignancies; however, studies relating to this did not take into account drugs used in modern regimens for rectal cancer. As such, the most problematical long-term side effect is peripheral neurotoxicity secondary to oxaliplatin.

5.2.4. Monoclonal Antibody Therapy

Blockade of both VEGF and EGFR with monoclonal antibodies has proven to be helpful in advanced colorectal cancer [Van Cutsem et al, 2009; Bokemeyer et al, 2009; Cunningham et al, 2004; Van Cutsem et al, 2007; Jonker et al, 2007; Hurwitz et al, 2004]. Bevacizumab, a VEGF antibody, has been integrated into neoadjuvant CRT with variable toxicity and pCR rates (0% - 32%), but reports so far are limited to small numbers and no solid conclusions concerning its additional benefit can presently be drawn [Willett et al, 2009; Crane et al, 2010; Resch et al, 2010]. Two recent studies have added bevacizumab to neoadjuvant chemotherapy before CRT, again with small numbers. The Avacross single-arm study [Nogue et al, 2009] administered 4 cycles of CAPOX plus bevacizumab before CRT with capecitabine plus bevacizumab in 47 MRI-defined high risk patients with inclusion criteria similar to those of the EXPERT trial. Ninety-three percent underwent surgery with 38.6% achieving a pCR (95% CI, 24.7-54.5). DiPetrillo et al [2008] combined bevacizumab with FOLFOX6 for 2 cycles before CRT (delivered with bevacizumab, oxaliplatin, and capecitabine) and surgery with 23 patients at the time of reporting. Five patients achieved a pCR, but toxicity was an issue during the CRT phase with 75% developing moderate to severe toxicity.

A further study recruited 31 patients with FOLFOX plus bevacizumab followed by surgery [Schrag et al, 2010]. No pre-operative RT was given. A pCR rate of 27% was observed.

The incorporation of anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab, into the management of rectal cancer patients has been evaluated in a number of phase I and II studies because of their proven effectiveness in patients with advanced disease not harboring a Kirsten-RAS (K-RAS) gene mutation. Cetuximab is a known radiosensitizer, and its addition to neoadjuvant CRT is viable; still, in phase I and II studies of unselected populations to date, no improvements in clinical outcomes have been demonstrated [Machiels et al, 2007; McCollum et al, 2010].

The EXPERT-C phase II trial randomized patients to the EXPERT treatment regimen with our without cetuximab, delivering the antibody therapy during both the neoadjuvant chemotherapy and CRT treatment phases, rather than using it purely as a radiosensitizer [Dewdney et al, 2011]. Between 2005 and 2008, 164 patients were recruited. Among those with K-RAS and B-RAF wild type tumors, radiological response rates were significantly better with the addition of cetuximab to neoadjuvant chemotherapy (50% vs. 70%; $P = 0.038$) and CRT (72% vs. 89%; $P = 0.028$). In addition, a significant improvement in overall survival was observed with the addition of cetuximab (HR: 0.27; $P = 0.035$).

5.3. Adjuvant Therapy

Distant failure rates remain as high as 36% with neoadjuvant CRT alone, deeply contributing to the lack of survival benefit of this approach [Sauer et al, 2004]. Therefore, intensification of the systemic component of management is desirable, and chemotherapy without RT has been evaluated in the adjuvant setting. A number of studies have revealed a survival benefit with adjuvant chemotherapy [Fisher et al, 1988; Krook et al, 1991; Tepper et al, 2002; Wolmark et al, 1993]. In a pooled analysis of 5 phase III trials, overall survival was significantly improved by adjuvant chemotherapy either alone, as part of a CRT regimen, or as maintenance in addition to CRT compared with surgery alone or surgery plus adjuvant RT ($P < 0.0001$) [Gunderson et al, 2004].

The QUASAR (Quick and Simple and Reliable) trial of adjuvant fluorouracil (5-FU) plus folinic acid in stage II colorectal cancer included 948 patients with resected rectal cancer, 21% of whom received neoadjuvant RT [Quasar Collaborative Group, 2007]. Adjuvant chemotherapy provided a modest overall survival benefit for stage II colorectal cancer; in the subset analysis of rectal cancer patients who received neoadjuvant RT, chemotherapy significantly reduced the risk of recurrence (HR = 0.68; 95% CI, 0.48-0.96) but not death (HR=0.77; 95% CI, 0.55-1.08).

The European Organization of Research and Treatment of Cancer (EORTC) Radiotherapy Group assessed the addition of 5-FU plus leukovorin to RT plus surgery in a 4-arm design, randomizing 1,011 patients to get either preoperative RT alone or CRT with or without postoperative chemotherapy [Bosset et al, 2006]. No difference was seen with the addition of preoperative chemotherapy to RT, and although there was a trend toward improved overall survival with postoperative chemotherapy, it did not reach statistical significance (5-year overall survival, 67.2% vs. 63.2%; $P = 0.12$). An exploratory subgroup analysis of those patients achieving an R0 resection showed that in the event of significant downstaging (ypT0-2 tumors) by preoperative treatment, adjuvant chemotherapy improved both disease-free survival (HR = 0.64; 95% CI, 0.45-0.91; $P = 0.013$), and overall survival (HR=0.64; 95% CI, 0.42-0.96; $P = 0.030$). No benefit was seen in the population without downstaging [Collette et al, 2007].

Because of the modest benefit with single-agent chemotherapy, routine care has more recently incorporated combined fluoropyrimidine/oxaliplatin adjuvant chemotherapy for high-risk individuals, extrapolating data from the colon cancer adjuvant NSABP C07 [Wolmark et al, 2008] and MOSAIC [Andre et al, 2004] studies.

Chapter II

Imaging rectal cancer

1. DIAGNOSIS

The diagnosis of rectal cancer is usually achieved by means of digital examination and endoscopic methods which include biopsy samples of the lesion. Occasionally, though, imaging techniques such as barium enema (Figure II.1) or CTC may be responsible for the detection of neoplastic lesions in the rectum.

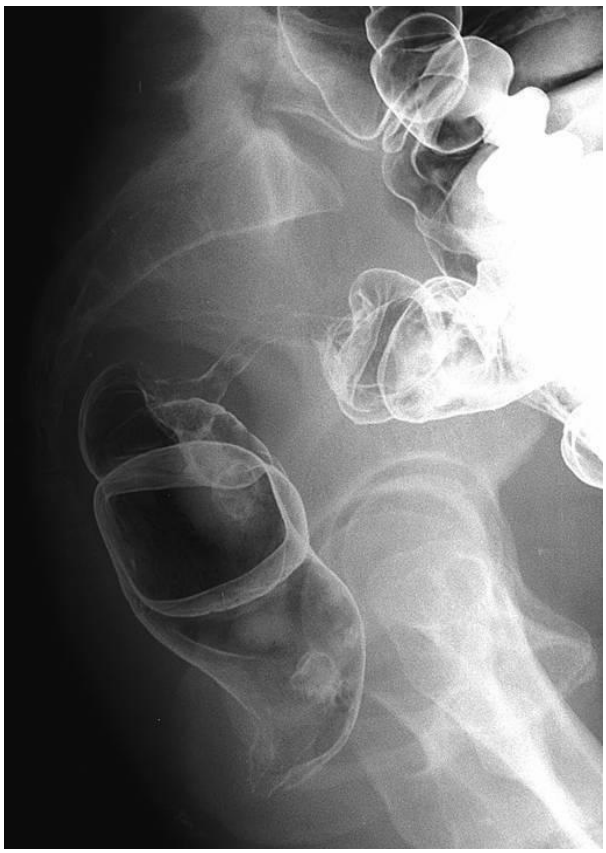


Figure II.1. Double contrast enema demonstrates a narrowing of the upper third of the rectum, with irregular borders and shouldering (the classical 'apple-core' appearance), consistent with a rectal carcinoma.

The double contrast enema is based on the instillation of a barium sulphate suspension and of its evacuation followed by inflation of air, with double contrast examination of the colon. A perfect colonic cleansing is a fundamental prerequisite, its inadequacy being one of the major causes of non-diagnostic examinations [Tinetti et al, 1989]. Indications for the procedure are the same as those for colonoscopy. Absolute contraindications for barium enema are: pregnancy; toxic megacolon; suspected colonic perforation; immediately preceding an endoscopic exam, especially

if with biopsy; acute diverticulitis or peritonitis; acute colonic obstruction; peritoneal fistulae, anatomical malformations (malrotation, hernia); and ischaemic colitis.
The strong points of barium enema are represented by: (1) concomitant visualization of the whole length of the viscus; (2) stenotic portions do not constitute an obstacle; (3) it allows functional assessment of the bowel; (4) radiographs enable an objective documentation of the lesions.
Technical limitations are for the most part due to fecal residues or artifacts (flocculation of barium, gas bullae) which may mimic true lesions such as inflammation, ulcerations or polyps. The most severe complication is undoubtly perforation, which in most cases involves the rectum and is associated to the air inflation, especially when balloon catheters in a diseased rectum are used.
In a report from the literature, 15% of the lesions missed by rectal exploration and rectoscopy and were detected during a barium enema [Evers et al, 1981]. However it can be affirmed that both exams miss some lesions and that in the rectum the two methods show a similar sensitivity in the identification of neoplasms [Kelvin et al, 1981; Miller et al, 1978].
As for CTC, it can similarly detect rectal lesions with ease, although some pitfalls have been reported [Mang et al, 2007].
The cross-sectional methods [CT and Magnetic Resonance Imaging (MRI)] are particularly useful for tumoral staging, but occasionally may permit detection of a rectal cancer.
Primary rectal tumors on CT may appear as an intraluminal focal mass or a plaque thickening of the viscus wall. The normal thickness of the rectal wall is less than or equal to 3 mm [Becker et al, 1986]. Focal or diffuse thickening should categorically point toward a neoplastic disease when the wall is over 5–6 mm thick [Thoeni, 1989; Angelelli et al, 1990]. However, most lesions are over 2 cm [Becker et al, 1986]. The CT attenuation of the neoplastic tissue is about 40–60 Hounsfield Units, usually slightly hypodense when compared to the normal wall (Figure II.2).

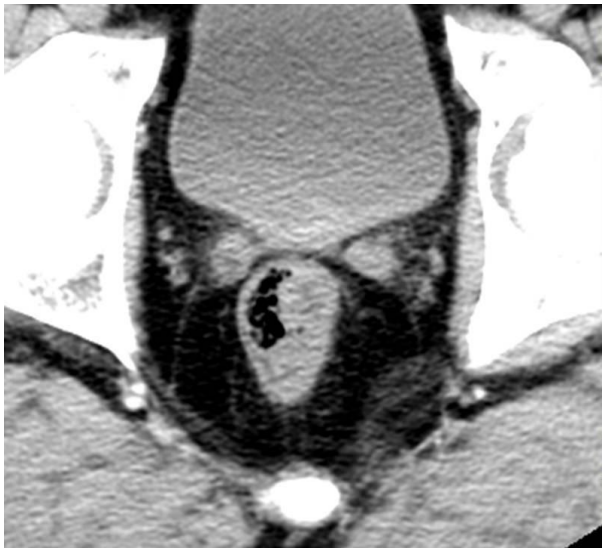


Figure II.2. CT image of a patient with rectal cancer shows a slightly hypodense and heterogeneous asymmetric thickening of the left rectal wall.

On MRI, carcinomas appear as wall lesions exhibiting a signal intensity which is somewhat higher than that of the muscularis propria on T2-weighted (w) images (Figure II.3a). High signal intensity of the tumor on T2-w images suggests the presence of mucinous carcinoma (Figure II.3b).

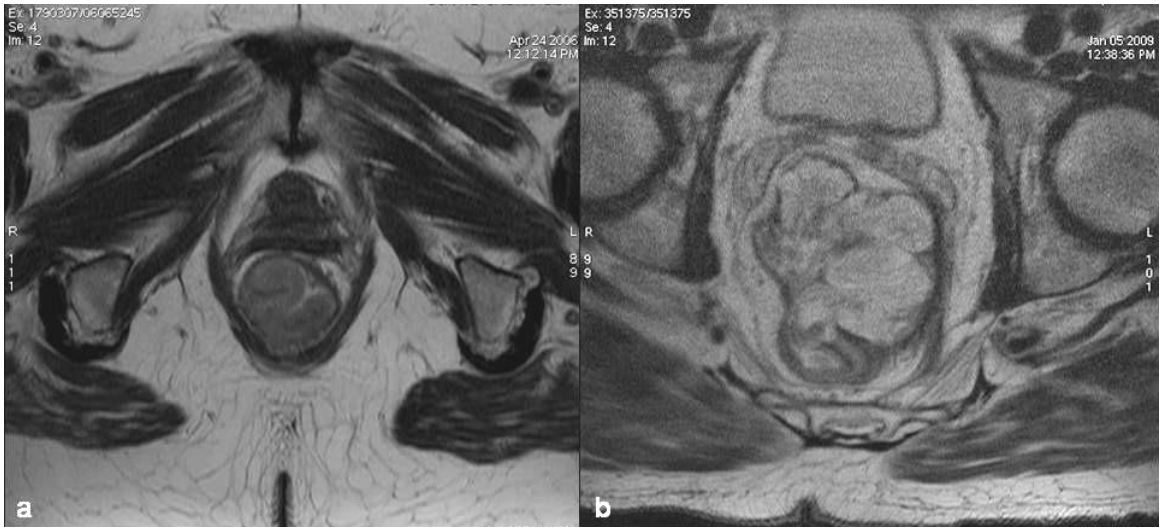


Figure II.3. Axial T2-weighted MR images of two patients with rectal cancer. On (a) the tumor shows an intermediate signal intensity, higher than that of the hypointense muscularis propria. On (b) the neoplasm is markedly hyperintense, which is consistent with a mucinous-type cancer.

Diffusion-weighted (DW)-MRI is based on the dephasing effect by the Brownian motion of extracellular water molecules. At DW-MRI, high signal intensity (diffusion restriction) on high b value DW MR images reflects high cellular density which is suggestive of a malignant lesion (Figure II.4b). The apparent diffusion coefficient (ADC) is the quantitative parameter of diffusion in DW-MRI, with a low ADC value reflecting diffusion restriction in a viable tumor (Figure II.4c).

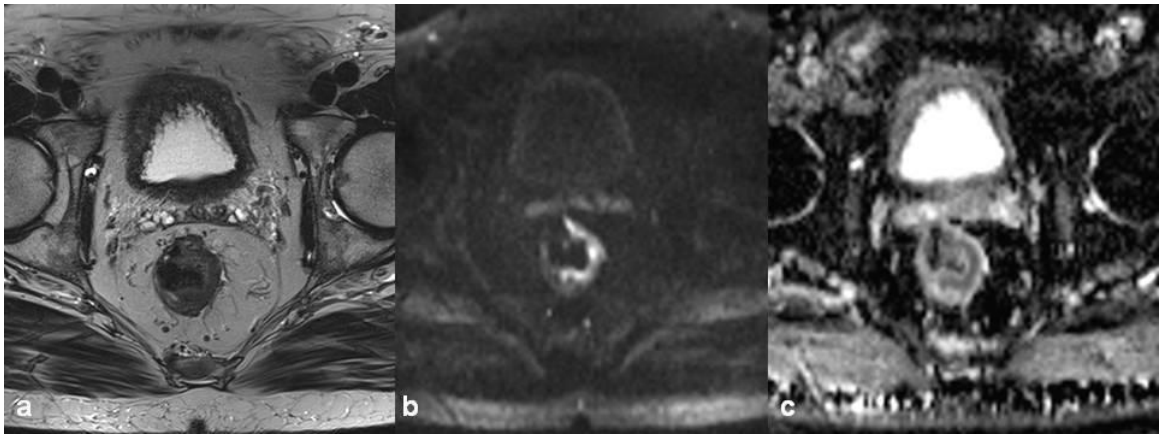


Figure II.4. Axial MR images of a patient with rectal cancer. On T2-w image (a) the tumor shows intermediate signal intensity, higher than that of the hypointense muscularis propria. On DWI ($b=1000 s/m^2$, b) the neoplasm is markedly hyperintense, with diffusion restriction, which is confirmed by a low ADC on the ADC map (c).

A recent study has shown the potential interest of high b value DW-MRI in detection of colorectal cancer [Hosonuma et al, 2006]. A report on the detectability of rectal cancer with T2-w imaging combined with DW imaging (DWI) (sensitivity, 93%–95%; specificity, 95%–100%; PPV, 97%–100%; NPV, 86%–91%) showed better detection of rectal cancer than with T2-w imaging alone (sensitivity, 82%–84%; specificity, 85%–90%; PPV, 92%–95%; NPV, 68%–72%) [Rao et al, 2008].

Positron Emission Tomography (PET)-CT is not recommended as the first choice examination for the initial diagnosis of rectal cancer, due to the low specificity (less than 50%) – resulting

from the high number of false-positive results secondary to bowel radiotracer uptake, inflammatory conditions, and/or radiotracer stasis during the elimination process – despite its high sensitivity that can exceed 95% [Delbeke and Walker, 2010].

2. LOCAL STAGING

The prognosis of rectal cancer strongly depends on several factors that have routinely been assessed by histopathological examination. These factors comprise the depth of tumor invasion into and beyond the bowel wall [Harrison et al 1994; Willett et al 1999], the number of lymph nodes involved with tumor [Wolmark et al 1986; Tang et al 1995], extramural venous invasion (EMVI) [Talbot et al. 1980], involvement of the CRM [Adam et al 1994], and the presence of ulceration of the peritoneum by tumor [Shepherd et al. 1995]. Accurate preoperative assessment of these prognostic factors is a pivotal prerequisite for selecting patients for neoadjuvant therapy and planning surgical approach to optimize complete excision [Barrett, 1998].
As such, in order to improve patient selection for individually tailored therapies, a trustworthy imaging modality that should be able to differentiate early-stage tumors from advanced tumors is warranted. A variety of examinations have been used for the preoperative evaluation of rectal cancer, including EUS, CT and MRI (Mathur et al, 2003).

2.1. Mesorectal fascia status

The main challenge for radiological staging today is to address accurately the relationship between the tumor and the MRF, which determines the status of the CRM, since the MRF corresponds to the dissection plane in TME surgery (Figure II.5).

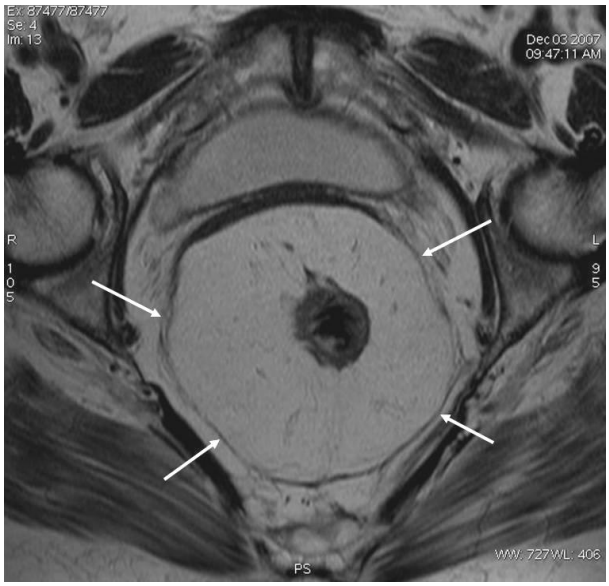


Figure II.5. Axial T2-weighted MR image clearly depicting the MRF, which appears as a hypointense linear structure (white arrows) encircling the mesorectal fat and the rectum.

Some authors suggest that CRM status, in combination with lymph node status, provides a better prognostic model than the existing TNM system [Nagtegaal et al, 2007; Gosens et al, 2007; Leite et al, 2011]. A study of 686 patients undergoing TME showed that local recurrence was only 5% in those with a disease-free CRM as opposed to 22% if infiltrated [Schnall et al, 1994]. Histopathology of resected specimens has revealed that the frequency of local recurrence significantly decreases when a tumor-free CRM greater than 1 mm can be obtained [Adam et al, 1994; de Haas-Kock et al, 1996; Quirke et al, 1986].
It has been proved that MRI provides detailed and accurate information about CRM status [Brown et al, 2003a].
Beets-Tan et al [2001a] reported that the prediction of MRF involvement was addressed with excellent interobserver agreement, thus allowing an MRI disease-free distance of 5 and 6 mm to correspond to a histopathological disease-free margin of 1 and 2 mm, respectively. Another study in 43 patients not only confirmed a high accuracy (95%) for prediction of CRM status but in addition showed in cadavers that the thin linear structure seen on MRI indeed corresponds to the MRF [Bissett et al, 2001]. One study in 98 patients with rectal cancer showed 92% agreement between MR images and histological findings for prediction of the CRM [Brown et al, 2003a].
Since sometimes staging (particularly T staging and specifically the differentiation between some T2 and T3 tumors) will not appreciably affect or alter the overall preoperative or operative management of the patients, the clinically pertinent benefit of MRI is the assessment of the distance from the tumor to the MRF which will is strongly predictive of local recurrence [Wibe et al, 2002; Nagtegaal et al, 2002] (Figure II.6).

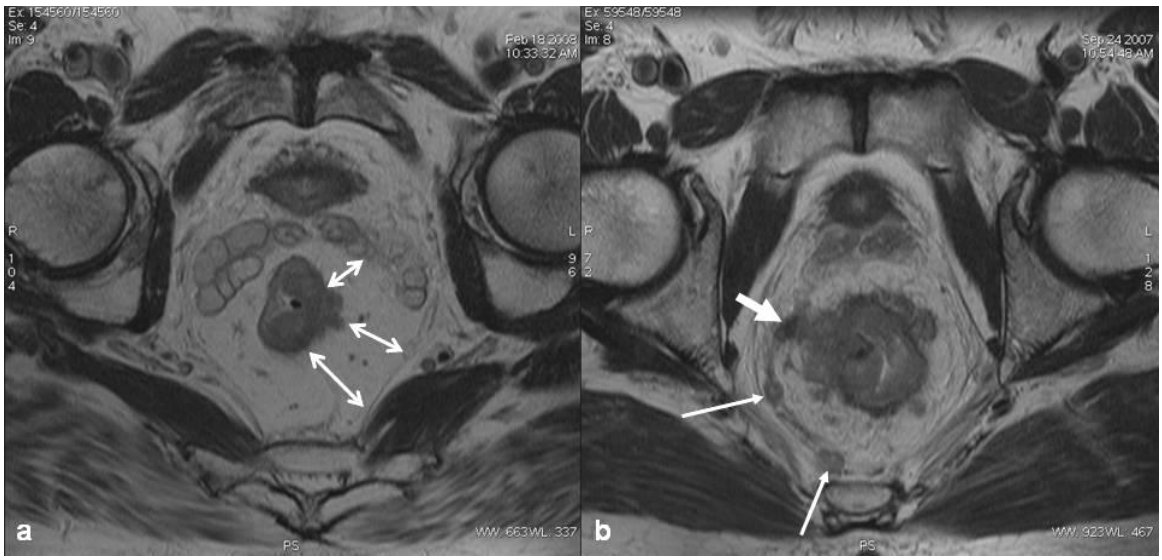


Figure II.6. Axial T2-weighted MR images of two patients with rectal cancer, both staged as T3. On (a) the tumor extends beyond muscularis propria but does not reach the MRF (double arrows). On (b) the neoplasm is invading the MRF (thick arrow) and there are some tumoral deposits within the MRF itself (thin arrows).

Despite the widely accepted efficiency of MRI in estimating the infiltration of the MRF by tumor, there is still some debate about the definition of MRI prediction of CRM involvement. Various earlier works have proved that tumor within 1 mm of the CRM on the resected specimen in rectal cancer surgery is a powerful predictor of local recurrence and poor survival [Quirke et al, 1986; Birbeck et al, 2002; Cawthorn et al, 1990; Wibe et al, 2002; Nagtegaal et al, 2008; Adam et al, 1994]. However, there is no consensus about the MRI criteria for an involved margin: the

study by Beets-Tan showed a correlation between a measured MRI distance of more than 5 mm to the MRF and subsequent negative CRM on histopathology [Beets-Tan et al, 2001a], whereas the Mercury study demonstrated that histopathologically negative margins could be predicted using a 1-mm cut-off and additionally showed that this was reproducible across 11 different centres with 18 distinct radiologists [MERCURY Study Group, 2006]. These variations have led to differences in the selection criteria of patients for preoperative CRT.

In a very recent study by Taylor et al. [2011], in which positive margin and local recurrence rates were compared for MRI distances from the tumor to the MRF of 1 mm or less, more than 1 mm up to 2 mm, more than 2 mm up to 5 mm, and more than 5 mm, the authors have reached the conclusion that a margin of 1 mm or less measured by MRI correlates accurately with pathological CRM involvement and poor outcome and thus constitutes the best cut-off distance for predicting CRM involvement using MRI. The use of a cut-off greater than 1 mm does not improve the accuracy of MRI in predicting CRM status, but would have resulted instead in substantial overtreatment that would achieve only minimal gain based on very low local recurrence rates observed following TME surgery. The rate of pathological CRM positivity was 53% in the group with a margin of 1 mm or less defined by MRI, and fell to 7 – 8% when the tumor distance to the MRF was greater than 1 mm but no more than 5 mm. The 5-year local recurrence rate for patients classified as CRM-positive on MRI using a cut-off 1 mm or less was 20%, compared with 4 – 8% in those with larger margins, giving a significantly worse hazard ratio. Nevertheless, CRM status is not the only factor involved in the prediction of local recurrence [Taylor et al, 2009] and it is well recognized that some patients develop local recurrence despite having an uninvolved margin [Wibe et al, 2002; Quirke et al, 2009; Merkel et al, 2001]. In this same study, up to 8% of patients developed a local recurrence despite possessing a free CRM.

Wolberink et al [2007] reported in a retrospective study of 125 patients with and without a short course of RT on the value of conventional CT in predicting MRF invasion. The area under the curve (AUC) of the receiver-operator-characteristics (ROC) curve ranged between 0.697 and 0.813, the sensitivity was just below 50%, and the majority of false negatives occurred in tumors located in the distal anterior rectum. Similarly, Vliegen and co-workers [2008a] evaluated the accuracy of multidetector (MD)-CT for the prediction of tumor invasion of the MRF, with MRI as reference standard. They found poor accuracy (54–66%), low AUCs (0.62–0.71) and high inconsistency among observers for the prediction of tumor invasion of the MRF. Evaluation of the staging accuracy of CT at different anatomical locations showed very poor AUCs (0.31–0.50) for low-anterior tumors, but the performance significantly improved for mid-high lateral-posterior located rectal tumors (AUC: 0.84–0.88; $P < 0.04$).

2.2. T Staging

Preoperative T staging of a rectal tumor by imaging is a complex task. At present, there is no widely accepted protocol on the role of diagnostic imaging in the preoperative T staging of rectal cancer.

Even if the present T-staging system is sometimes used for clinical decision making, it has its shortcomings, for it does not discriminate between tumors with a wide CRM and tumors with a close or involved CRM. Although most of these tumors are classified in the same stage (T3), they have a completely different risk for local recurrence. Moreover, it has been repeatedly shown that the distance from the tumor to the CRM is a more powerful predictor for the local

recurrence rate than is the T stage [Wibe et al, 2002; Nagtegaal et al, 2002; Quirke et al, 1986; Heald and Ryall, 1986].

The successful introduction of MRI for pelvic diseases has, in recent years, led to the steady role of this imaging modality for local and regional staging of rectal cancer. Initial studies on MRI were performed with a body coil, but because conventional body coil techniques showed a resolution that was still unsatisfactory to distinguish between the different layers of the rectal wall, overall accuracies reported for MRI with a body coil were relatively low, with values varying from 59% to 88% [Hodgman et al, 1986; Cova et al, 1994; Zerhouni et al, 1996; Butch et al, 1986; Guinet et al, 1990; Okizuka et al, 1993; Starck et al, 1995]. The introduction of endoluminal coils improved image resolution and made a detailed evaluation of the layers of the rectal wall possible [Vogl et al, 1998]. This was also reflected in improved and more consistent T staging, with accuracy ranging between 71% and 91% [Gualdi et al, 2000; Maldjian et al, 2000; Chan et al, 1991; Schnall et al, 1994; Indinnimeo et al, 1996; Zagoria et al, 1997; Pegios et al, 1996; Vogl et al, 1997]. Endorectal MRI can be very accurate for staging of superficial tumors, as shown in studies comparing it to endorectal ultrasound (EUS) [Gualdi et al, 2000; Maldjian et al, 2000; Zagoria et al, 1997]. However, some problems remain with endorectal MRI. Besides the limited availability and high cost, MRI with an endoluminal coil, especially when solely used, has a limited field of view. Like EUS, the MRF and surrounding pelvic structures are difficult to visualize owing to the sudden signal drop-off at a short distance from the coil [deSouza et al, 1996]. Furthermore, the positioning of an endoluminal device can be difficult or impossible in patients with high and/or stenosing tumors, and failed insertion rates of as high as 40% have been reported [Hunerbein et al, 2000].

The development of phased-array coils, gradients and pulse sequences obviated the need for endorectal coils with a predicted improvement in MRI performance [Beets-Tan et al, 1999; Beets-Tan et al, 2001b; Beets-Tan et al, 2001c; Brown et al, 1999; Blomqvist et al, 2000]. The advantages of high spatial resolution techniques with a large field of view make MRI with phased-array coils appropriate for staging of both early-stage and advanced rectal tumors. An optimized MRI technique should include sagittal T2-w turbo spin-echo sequences through the pelvis to detect the tumor, and then high-resolution T2-w examinations perpendicular to the tumor's long axis and in coronal plane, parallel to the tumor's long axis. Axial T1-w images of the entire pelvis may be used for detecting lymphadenopathy.

However, authors of the first studies on MRI with the multiple surface coil technique reported an overall accuracy for T staging of only 55%–65% and showed no benefit compared with the use of a body coil or even CT [Hadfield et al, 1997; de Lange et al, 1989]. The low performance of MRI in these studies could have been attributed to the low spatial resolution that was used with the early phased-array techniques. But even when a higher spatial resolution was applied with the new generation of phased-array coils, the accuracy for T staging was not as high as anticipated, with values varying between 65% and 86% [Blomqvist et al, 2000; Blomqvist et al, 1997, Beets-Tan et al, 2001a; Gagliardi et al, 2002], and was not as reproducible as expected, with considerable interobserver variability [Beets-Tan et al, 2001a] (Figure II.7).

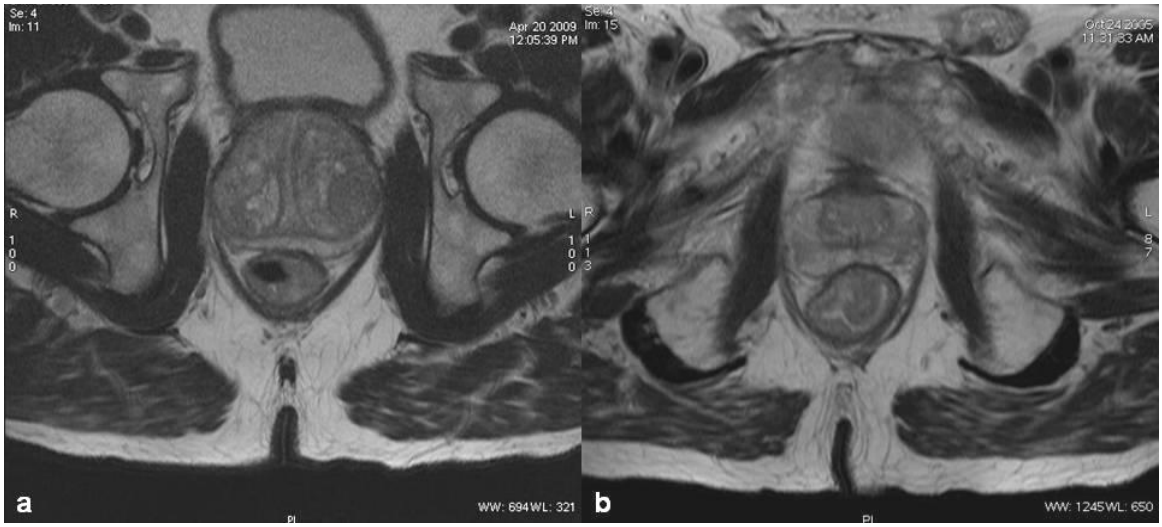


Figure II.7. Axial T2-weighted MR images of two patients with low rectal cancers staged as pT1 (a) and pT2 (b). The distinction between the two stages is virtually impossible by MRI with phased-array coils, as both tumors possess a similar appearance. However, MRI may suggest that these are both tumors limited to the rectal wall, as there is integrity of the hypointense muscular layer of the rectum.

One exception to the above was the study by Brown and colleagues [1999], who reported 100% accuracy and complete agreement between two readers on the prediction of tumor stage with phased-array MRI.

The use of an intravenous gadolinium-based contrast agent is not generally established as an adjunct to local staging of rectal cancer. Vliegen et al [2005] reported that the addition of gadolinium-enhanced T1-w MRI sequences to T2-w fast spin-echo sequences did not significantly improve the diagnostic accuracy for the assessment of tumor penetration through the rectal wall. Okizuka et al [1996] also found no improvement in T staging after adding a gadolinium-enhanced fat-suppressed sequence to conventional T1- and T2-w images.

Important MRI criteria relevant for the vast majority of rectal neoplasms are summarized in accordance with the findings of Brown et al [2003a] as follows:

- *Stage T1*: low signal in the submucosal layer, replacement of the submucosal layer by abnormal signal not extending into the muscle coat
- *Stage T2*: intermediate SI within muscularis propria
- *Stage T3*: broad-based bulge or nodular projection or intermediate SI projecting beyond outer muscle coat
- *Stage T4*: extension of abnormal signal into adjacent organ, extension of tumor signal through the peritoneal reflection

Therefore, the outermost margin of the muscularis propria will remain intact with stage T2 tumors or less (Figures II.7 and II.8).

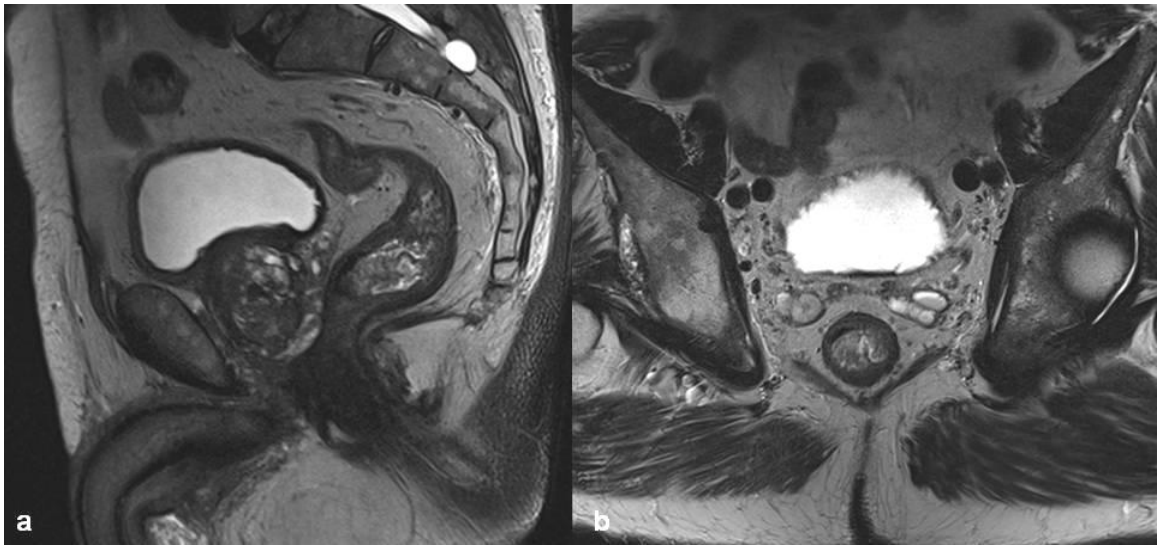


Figure II.8. Sagittal (a) and axial (b) T2-weighted MR images of a patient with a stage pT2 rectal cancer, showing integrity of the hypointense muscular layer.

Differentiation between T2 and T3 tumors may be difficult, however [Beets-Tan et al, 2001a; Brown et al, 1999]. In fact, most staging failures with MRI occur in the differentiation between T2-stage and borderline T3-stage lesions, with overstaging as the main cause of errors, often caused by desmoplastic reactions [Vogl et al,1997; Brown et al, 1999; Beets-Tan et al, 2001a; Meyenberger et al, 1995], since it is difficult to distinguish on MR images between spiculation in the perirectal fat caused by fibrosis alone (stage pT2) and spiculation caused by fibrosis that contains tumor cells (stage pT3) [Beets-Tan et al, 2001a]. Underestimation is generally attributable to microscopic invasion which is basically undetectable on MRI [Akasu et al, 2005] (Figure II.9).

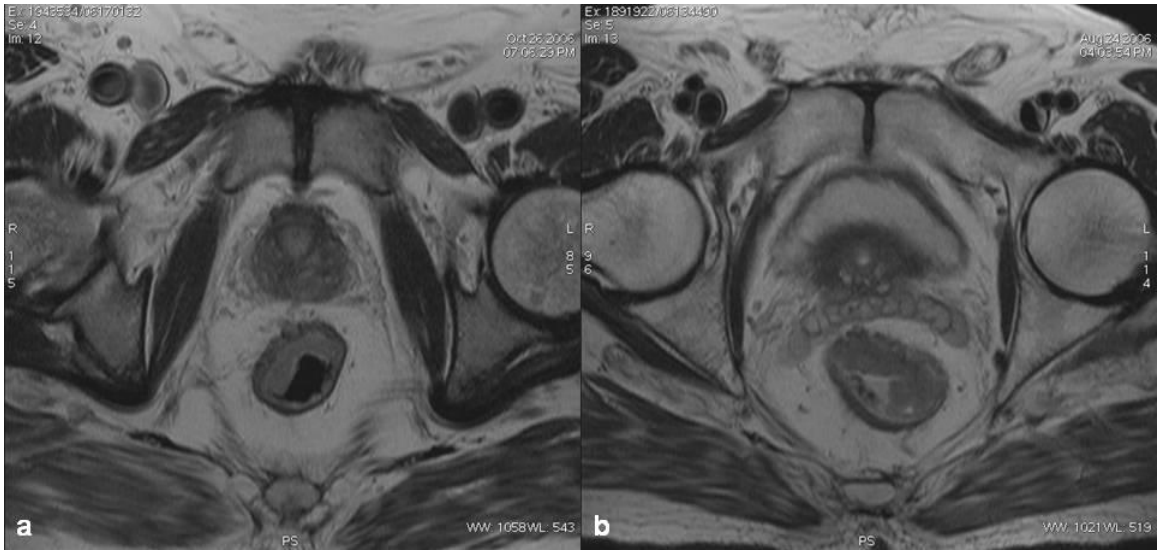


Figure II.9. Axial T2-weighted MR images of 2 patients with rectal cancers staged as pT2 (a) and borderline pT3 (b). A considerable similarity of the MR appearance of both tumors is noted, illustrating the difficulties of imaging in differentiating between tumors limited to the rectal wall (a) and tumors with microscopic invasion of the mesorectal fat (b).

However, differentiating between minimal T3 infiltration and T2 lesions is probably of little consequence for patient management, as patients with minimal T3 infiltration into perirectal fat

are also at low risk of surgical failure from CRM involvement [Cawthorn et al, 1990; Chung et al, 1983].
Conversely, the depth of tumor invasion is known to be an important prognostic factor in rectal carcinoma [Hermanek et al, 1995; Park et al, 1999]. The prognostic heterogeneity of these pT3 rectal cancer patients has been recognized in a number of studies [Cawthorn et al, 1990; Krook et al, 1991; Willett et al, 1999]. In the Erlangen Registry of Colorectal Carcinomas (ERCRC) series, patients with rectal cancer invading beyond the border of the muscularis propria 5 mm or less (pT3a) had a more favorable prognosis than those with invasion greater than 5 mm (pT3b) when considering local recurrence and cancer-related survival. The local recurrence rate was 10% for pT3a and 26% for pT3b. Statistically significant differences in cancer-related 5-year survival rates were found between pT3a and pT3b (85% vs. 54%). The analysis of the ERCRC data also confirmed that some lymph node-negative pT3 patients had results similar to pT2 patients. For node-negative pT3 patients with less than or equal to 5 mm of invasion beyond the muscularis propria (pT3a) and for node-negative pT2 patients, the local recurrence rates were 10% and 9%, with 5-year survival rates of 91% and 94%, respectively [Merkel et al, 2001].
Stage T4 tumors are diagnosed by depicting infiltration into an adjacent organ (Figure II.10).

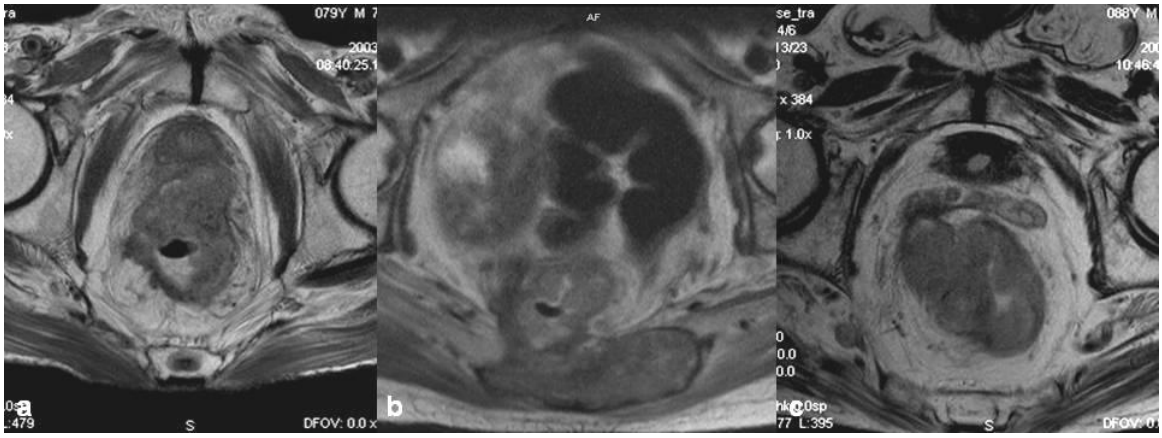


Figure II.10. Axial T2-weighted MR images of 3 patients with rectal cancers staged as T4. On (a) there is invasion of the prostate gland. On (b) the tumor is extending posteriorly, invading the sacral spine. On (c) there is invasion of the right seminal vesicle.

Endorectal ultrasound is helpful in determining the depth of invasion of early-stage disease [Rifkin et al, 1989; Hunerbein, 2003]. The degree to which the tumors disrupt and penetrate the rectal wall layers suggests the local stage. T1 tumors do not penetrate the hypoechoic muscularis propria and the preservation of a bright sonographic layer medial to the muscularis represents an intact submucosa. T2 tumors penetrate the muscularis propria and so merge with it. T3 tumors extend beyond the muscularis propria and infiltrate the perirectal fat to a variable degree.
EUS is nowadays the most accurate imaging method for the assessment of tumor ingrowth into rectal wall layers, with accuracies for T staging ranging between 69% and 97%, [Beynon et al, 1986; Glaser et al, 1990; Katsura et al, 1992; Herzog et al, 1993; Hulsmans et al, 1994; Akasu et al, 1997; Milsom and Graffner, 1990; Lee et al, 1999; Garcia-Aguilar et al, 2002; Genna et al, 2000; Gualdi et al, 2000; Kim et al, 1999; Massari et al, 1998; Sailer et al, 1997; Marone et al, 2000; Maldjian et al, 2000; Akasu et al, 2000]. In a meta-analysis [Solomon and McLeod, 1993] of 11 studies, sensitivity was shown to be affected by T stage. Despite being very accurate for staging of superficial rectal tumors, EUS is not as useful for staging advanced rectal cancers. A large study on the use of the technique in 1,184 patients with rectal tumors confirmed these

findings [Garcia-Aguilar et al, 2002]. The overall staging accuracy of 69% for EUS in that study was lower than previously reported values because the limited depth of acoustic penetration prevents accurate assessment of local tumor extent in bulky T3 and advanced rectal cancers. The discrepant results of that study may be attributable to the operator-dependent nature of US and the substantial interobserver variability, which was also reported in former studies on EUS [Garcia-Aguilar et al, 2002; Enck et al, 1997; Gold et al, 1999; Solomon et al, 1994]. Furthermore EUS cannot consistently visualize the MRF and thus cannot indicate whether the planned surgical CRM will be clear from tumor. Other limitation of EUS is the inability to pass the probe through large obstructing tumors. For all the above reasons, EUS has not been widely adopted as the preferred imaging modality for preoperative local staging of rectal cancer.

Initial studies with conventional CT [Thoeni et al, 1981; Zaunbauer et al, 1981; van Waes et al, 1983; Grabbe et al, 1983; Rotte et al, 1989; Hodgman et al, 1986] mainly focused on locally advanced rectal cancer, and high accuracies for T staging were reported to vary between 79% and 94%. However, later studies [Rifkin et al, 1989; Kim et al, 1999; Goldman et al, 1991; Cova et al, 1994; Shank et al, 1990; Zerhouni et al, 1996; Thoeni, 1997; Butch et al, 1986] that included less advanced tumors have shown accuracies that were not as high as anticipated previously, varying between 52% and 74%. In a meta-analysis of 78 studies conducted between 1980 and 1998 in 4,897 patients with rectal cancer, CT showed an accuracy of 73% for T staging [Kwok et al, 2000]. The low spatial and contrast resolution of conventional CT does not permit a detailed evaluation of the rectal wall and may have contributed to the low performance of CT for staging superficial tumors.

The more recent MD technology allows for multiplanar imaging, but there are limited prospective studies to address a newer role for CT in this respect [Filippone et al, 2004]. Theoretically, the new generation MD-CT scanners, providing superior spatial resolution and multiplanar capabilities, are expected to offer better performance than conventional CT scanners [Chiesura-Corona et al, 2001; Horton et al, 2000]. In a study on 105 rectal cancer patients who underwent spiral CT [Chiesura-Corona et al, 2001], a superior overall accuracy for T staging (82%) was reported, but only four T4 tumors were included in that report. Although spatial resolution has improved considerably with MD-CT, its main limitation remains the intrinsic low contrast resolution.

When comparing MRI with CT, Blomqvist et al [1997] found superior performance for the former method in predicting bladder and uterine invasion. Beets-Tan et al [2000] compared phased-array MRI with CT in 26 patients with advanced or recurrent rectal cancer and found MRI to be far more accurate than CT in the assessment of organ invasion, pelvic wall invasion, and subtle bone marrow invasion. However, the large dissimilarity in outcome between the two modalities could be partly attributed to the fact that a state-of-the-art MRI technique was compared with conventional CT technique [Beets-Tan et al, 2000].

Considering the detail of T staging, PET / PET-CT is not useful for T-staging purposes because of its relatively low spatial resolution of around 5 mm, and its poor anatomic resolution compared with EUS and MRI [Grassetto et al, 2011].

2.3. N staging

The fact that nodal disease is a powerful prognostic indicator not only for distant metastases but also for local recurrence has been confirmed in the large Dutch TME trial, where patients with stage III (TxN1) disease had a 10-fold higher risk for local recurrence than did those with stage I

(T1–2N0 stage) disease and a threefold higher risk than did those with stage II (T3N0 stage) disease [Kapiteijn et al, 2001]. In addition, patients with stage N2 disease have a significantly higher risk of local recurrence compared with those with N0 or N1 disease [Moran et al, 1992].
Evaluation of surgical specimens indicates that rectal cancer most frequently spreads to the lymph nodes located in the mesorectal fat, and, to a lesser degree, along the superior rectal artery [Dworak, 1991; Steup et al, 2002] irrespective of whether the tumor arises from the upper, middle or lower third of the rectum. Koh et al [2005] demonstrated that the majority of mesorectal nodes associated with rectal cancer were found at the level of the primary tumor. The likelihood of metastases was also found to increase with the T stage of the tumor, occurring in up to 50% of patients with stage-T4 disease [Hida et al. 1997a].
Lateral tumor spread to pelvic sidewall nodes is a matter of some controversy. It has been suggested that pelvic sidewall nodal dissemination occurs in 10% to 25% of patients with rectal cancer [Hojo et al, 1982; Morikawa et al, 1994]. Lateral spread has been reported more often in patients with low rectal cancers [Hocht et al, 2002, 2004]. Involved nodes in the pelvic sidewall augment the risk of systemic dissemination [Ueno et al, 2001]. Not surprisingly, the 5-year survival in patients with pelvic sidewall lymph node metastasis is low (25–42%) [Ueno et al, 2001; Takahashi et al, 2000; Hida et al, 1997b]. Unlike mesorectal nodes, pelvic sidewall nodes are not routinely removed during TME surgery and extended lymphadenectomy may be required to achieve clearance of the tumor [Billingham, 1994; Suzuki et al, 1995].
When the treatment strategy is postoperative CRT for patients with N1 disease, there is little need to identify the lymph node status preoperatively. On the contrary, when the emphasis is on preoperative CRT and one wants to select patients at high risk, determination of lymph node status becomes vital.
Only approximately 65% of mesorectal nodes found by histopathology can be identified on *in vivo* MRI, and despite non-visualization of a substantial proportion of small mesorectal nodes, the incidence of malignancy in them is low [Koh et al, 2006].
However, identification and characterization of nodal disease is still a diagnostic challenge for the radiologist, and N staging can be considered the 'Achilles' heel' of rectal cancer imaging.
Despite the identification of lymph nodes as small as 2–3 mm on high-spatial-resolution MR images, reliable detection of nodal metastases is presently not achievable. The evaluation of nodal involvement normally relies on morphologic criteria such as the size and shape of the node [Jager et al, 1996; Williams et al, 2001; Carrington, 1998]. The dilemma with morphologic imaging, however, is that with enlarged nodes it is difficult to discriminate between reactive and metastatic nodes, and with small nodes micrometastases are easily missed. An additional problem in rectal cancer, as compared with other pelvic tumors, is the elevated frequency of micrometastases in normal-sized nodes [Monig et al, 1999; Andreola et al; 1996, Bjelovic et al, 1998; Dworak, 1989] (Figure II.11).

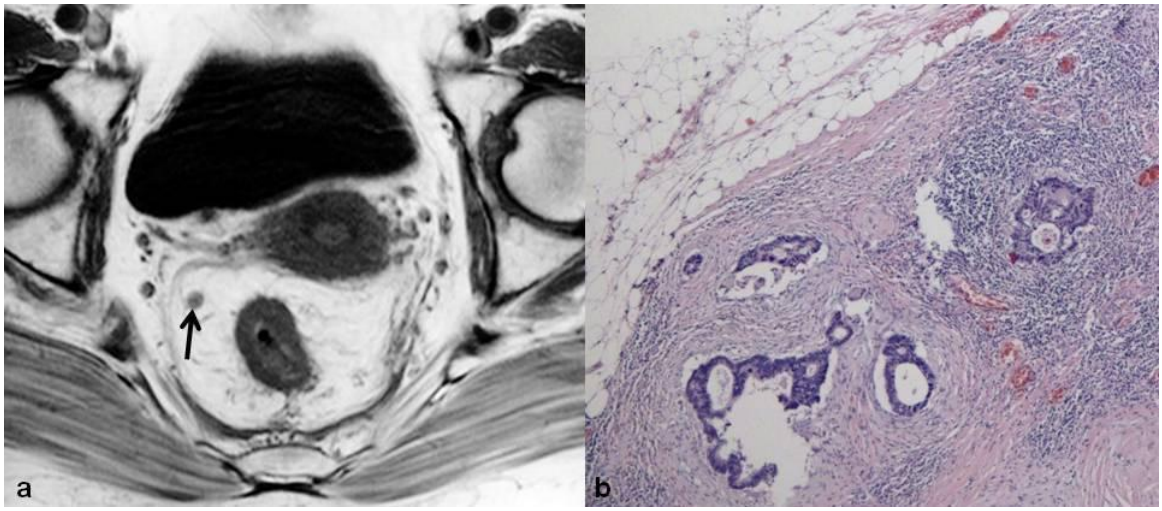


Figure II.11. Axial T2-weighted MR images of a patient with rectal cancer (a) depicting a small (< 5 mm), homogeneous and sharply-marginated mesorectal lymph node and H&E stain (b) of the same node, showing some microscopic islands of tumoral cells within it.

There has been limited success in the application of size criteria to determine the absence or presence of nodal disease. This is chiefly due to the fact that mesorectal nodes, whether benign or malignant, tend to be small. In a study of 424 surgical rectal specimens containing 12,759 nodes, the mean nodal diameter was 3.34 mm and the mean diameter of metastasis was 3.84 mm [Dworak, 1991]. In addition, nodal hyperplasia was common, which resulted in benign nodal enlargement. In another pathological study of 698 lymph nodes [Monig et al, 1999], 70 of 132 (53%) of nodes harboring metastases were < 5 mm in diameter.

Moreover, there is no consensus on the size criterion for prediction of metastatic nodes. In the reports of MRI studies, criteria used were: any detectable node [Maier et al, 2000; Okizuka et al, 1996; deLange et al, 1990], lymph nodes > 3mm [Vogl et al, 1997], lymph nodes > 5mm [Blomqvist et al, 1999; Gagliardi et al, 2002; Blomqvist et al, 2000; Thaler et al, 1994;], lymph nodes > 8mm [Kusunoki et al, 1994], and lymph nodes > 1 cm [Kim et al, 2000; Urban et al, 2000]. A cutoff value of 10 mm yields high specificity but low sensitivity [Zerhouni et al, 1996], whereas the reverse is true if a cutoff of 3 mm is employed [Vogl et al, 1997]. The citations of long- or short-axis diameter were also unclear in most articles and the accuracy widely ranged (43–85%).

In a meta-analysis of imaging studies used for staging rectal cancer, there were no significant differences among EUS, CT, and MRI in nodal staging [Bipat et al, 2004]. Many of these studies adopted size criteria of 5 mm in discriminating between malignant and benign nodes. Unsurprisingly, the application of a size criterion of 5 mm maximum short axis nodal diameter for discriminating between benign and malignant nodes has at best a moderate sensitivity and specificity for the detection of nodal metastases [Kim et al, 2000; Hadfield et al, 1997; Matsuoka et al, 2004]. EUS was found to have a sensitivity of 67% (95% CI: 60%–73%) and a specificity of 78% (95% CI: 71%–84%). CT was found to have a sensitivity of 55% (95% CI: 43%–67%) and a specificity of 74% (95% CI: 67%–80%). MRI was found to have a sensitivity of 66% (95% CI: 54%–76%) and a specificity of 76% (95% CI: 59%–87%).

The borders and the signal characteristics of lymph nodes on high–spatial resolution T2-w MRI sequences were found to be more accurate than nodal size in discriminating between benign and malignant nodes [Brown et al, 2003b; Kim et al, 2004]. Metastatic nodes have irregular borders or display heterogeneous signal intensity on T2-w sequences (Figure II.12).

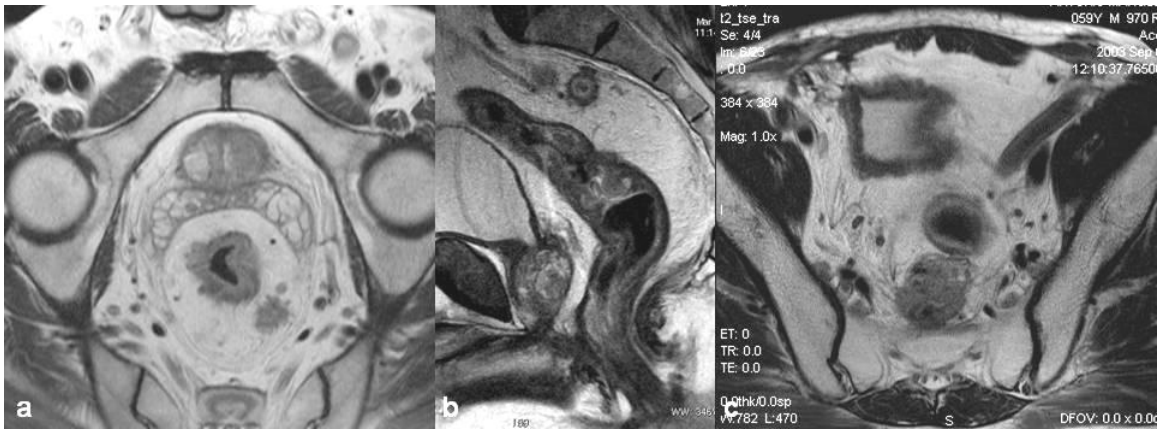


Figure II.12. Axial T2-weighted MR images of three patients with rectal cancer, showing large-sized metastatic mesorectal lymph nodes with irregular borders and heterogeneous signal intensities. In these situations, MRI can accurately assign them as metastatic.

Irregular nodal outline related to partial or complete nodal replacement with tumor results in gross distortion, and extranodal extension in incompletely involved nodes leads to irregularity of the surrounding capsule, while signal heterogeneity reflects tumor foci within the involved node, likely to contain areas of necrosis or extracellular mucin. If either of these criteria was present, a sensitivity of 85% (95% CI: 74%–92%) and a specificity of 97% (95% CI: 95%–99%) was achieved for detecting nodal metastases in nodes ≥ 3 mm [Brown et al, 2003b].

In a study by Kim et al [2004], spiculated and indistinct nodal borders on T2-w images were found to have 45% and 36% sensitivity, respectively, but 100% specificity.

The disparity in diagnostic accuracy when applying morphological criteria may be caused in part by difficulties and differences in interpreting nodal features. A normal node often has a low-signal-intensity nodal capsule on T2-w images that appears different from the nodal center and should not be misinterpreted as nodal heterogeneous signal intensity. Furthermore, reactive nodal hyperplasia can cause heterogeneous signal intensity on T2-w images, leading to an incorrect judgement of whether the node is metastatic or not. False-negative findings may be seen in partially replaced lymph nodes, resulting in no noticeable changes in nodal contour or signal intensity characteristics. Metastatic foci measuring 1–2 mm within nodes are presently impossible to detect because they are beyond the spatial resolution of the current MRI technique [Koh et al, 2010].

Using EUS, nodes measuring 2 to 3 mm in size can be resolved within the mesorectum [Rafaelsen et al, 1992]. A few studies found that the internal nodal architecture on sonography can discriminate between benign and malignant nodes [Katsura et al, 1992; Hildebrandt et al, 1990]. A key observation in EUS studies is that the internal texture of a node may correlate better with the presence of metastases than nodal size, and that inhomogeneity and hilar reflectivity are important discriminators of nodal status [Hildebrandt et al, 1990; Hildebrandt et al, 1995]. In fact, Katsura et al [1992] noted that the specificity of EUS could be improved if the echogenicity of a node was considered in addition to its size. Metastases were more common in nodes of mixed intranodal echogenicity than in those of uniform hyperechogenicity. However, other authors have found that it was impossible to discriminate between benign and malignant nodes based on nodal appearance [Rafaelsen et al, 1992].

Due to the lack of accuracy demonstrated by all the conventional imaging methods, 'functional' imaging has been gaining an increasing significance in the preoperative evaluation of mesorectal LN.

In this way, MRI with the administration of ultrasmall superparamagnetic iron oxide (USPIO) contrast agents has shown promising results for staging nodal metastases. These iron oxide particles are taken up by cells of the reticuloendothelial system of non-metastatic nodes [Mack et al, 2002; Weissleder et al, 1990; Tanoura et al, 1992; Guimaraes et al, 1994; Lee et al, 1991; McLachlan et al, 1994]. As it has been shown in prior studies, iron oxide deposition originates a decrease in the signal intensity in non-metastatic nodes due to the T2 shortening effects of iron, whereas metastatic nodes, devoid of macrophages, will not undergo signal intensity changes when using T2-w sequences [Weissleder et al, 1990]. Metastatic deposits appearing as white areas within the node as small as 2 mm could be identified in nodes deemed to be normal by both dimensional and morphological criteria [Koh et al, 2004].

A study by Lahaye et al [2008] demonstrated that an estimated area of white region within the node larger than 30% was highly predictive for a malignant node, with a sensitivity of 93% and a specificity of 96%. The larger the area of the white region, the more likely the node was metastatic. The white region in the lymph node was caused by no or very little uptake of USPIO in that malignant part of the node which is devoid of phagocytic capacity. Benign conditions such as focal nodal fibrosis, granulomatous disease, or fatty metaplasia, a feature that can be found in about 5% of nodes [Anzai et al, 1997; Van der Brekel et al, 1990] also can be depicted as a white region because of the lack of macrophages, thus mimicking malignant nodes. These white regions, however, usually do not occupy more that 30% of the nodal area [Lahaye et al, 2008].

A more recent study published by Koh et al [2010] could not replicate such high values of diagnostic accuracy: use of USPIO resulted in an average sensitivity of 65% (95% CI, 35–88%); specificity, 93% (87–96%); positive predictive value, 43% (21–67%); and negative predictive value, 97% (92–99%). Nevertheless, these authors used a range of patterns of contrast enhancement in order to discriminate between malignant and non-malignant lymph nodes, thus potentially introducing a certain level of subjectivity and creating a potential source of erroneous interpretation. However, this study also showed that USPIO-enhanced MRI had significantly higher ($P < 0.01$) diagnostic specificity than morphological MRI criteria alone [Koh et al, 2010]. Improvement in specificity could be due to a better classification of benign reactive lymph nodes. However, the lack of substantial improvement in sensitivity might be related to partially replaced and small involved mesorectal nodes which are beyond the resolution of the current imaging techniques to confidently detect small metastatic foci. In this way, the technique may be of value in identifying patients with node-negative disease who are being considered for local excision surgery.

A recent work by a Dutch group [Lambregts et al, 2011a] evaluated the value of a gadolinium-based contrast medium (gadofosveset) in the characterization of mesorectal lymph nodes in patients with rectal cancer. The authors showed that gadofosveset-enhanced MRI improved the diagnostic performance for nodal staging compared with standard MRI, attributed to both better detection and characterization of lymph nodes. Even though the exact mechanism is still unknown, it was proved that normal or reactive lymph nodes demonstrated gadofosveset uptake, inducing a strong increase in signal intensity which was comparable to that of neighboring blood vessels [Herborn et al, 2002; Lahaye et al, 2009a]. Due to this local increase in signal intensity, a ring-shaped artifact surrounding the lymph node was accentuated, creating the visual impression of a relief effect or "relief sign". In metastatic nodes, where tumor replaces normal lymphoid tissue, there was no gadofosveset uptake.

Therefore, in malignant nodes, dark areas corresponded to tumoral deposits. The "relief sign" was absent when the whole node was involved. These criteria—signal enhancement and nodal relief—were highly advantageous for a more accurate distinction between benign and malignant

lymph nodes. The high negative predictive value of more than 95% on a per lesion and more than 85% on a per patient basis for gadofosveset-enhanced MRI was equivalent to that of previous reports with USPIO [Lahaye et al, 2008; Koh et al, 2004; Will et al, 2006; Lahaye et al, 2009b]. The PPV was also in the same range as with USPIO: 70% to 80%.
DWI has not yet been shown to be valuable in characterizing lymph nodes in patients with rectal cancer. Although high b-value DWI is sensitive for detecting the location of lymph nodes, its characterization value is unproven in cancer, with necrotic neoplastic nodes yielding false-negative results and reactive hyperplastic nodes causing false-positive cases [Figueiras et al, 2010].
A recent study published in a surgery journal [Mizukami et al, 2011] examined patients with rectal cancer for nodal staging using DWI + conventional (T1-w and T2-w) MRI and CT. Results showed a clear benefit of MRI over CT: the overall patient-based sensitivity, specificity, PPV, NPV and accuracy of DWI + conventional MRI were 93, 81, 81, 93, and 87%, respectively, while corresponding values for CT were 73, 79, 74, 77, and 76%, respectively. The overall node-based sensitivity, specificity, PPV, NPV, and accuracy of DWI + conventional MRI were 97, 81, 52, 99, and 84%, respectively, whereas corresponding values for CT were 86, 80, 48, 96, and 81%, respectively. However, it is unclear from the study design which were the criteria used by the authors to differentiate normal from metastatic nodes, since these were considered to be soft tissue nodules with high signal intensity that were detected on DWI with their existence confirmed on T1-w and T2-w conventional MRI. It remains to be explained whether the signal intensity of normal nodes on DWI was different, since non-metastatic nodes are generally very cellular and may also cause restricted diffusivity.
Furthermore, despite the higher accuracy of MRI in this study, it remains to be known the real benefit, if any, of DWI (isolated or in combination with conventional sequences) over conventional MRI alone.
Although PET has substantially altered the landscape of oncologic practice in the last few years, it is unlikely that it can contribute to the visualization and characterization of mesorectal nodes. First, these are typically small and may be beyond the spatial resolution of the technique. Second, mesorectal nodes are most frequently found at the level of the tumor, and the avid metabolic uptake of the radioactive tracer within the primary lesion obscures visualization of the adjacent nodes. However, PET and PET-CT imaging could play a potential role in identifying lateral spread to nodes along the internal iliac chain [Koh et al, 2006].

2.4. Extramural venous invasion

Even in patients undergoing careful TME, venous invasion remains an important independent prognostic factor [Heald and Ryall, 1986; Bokey et al, 1999]. Extramural venous invasion (EMVI) is associated with higher risk of local recurrence [Rich et al,1983], distant metastases [Gunther et al, 2002; Krasna et al, 1988; Ouchi et al, 1996; Horn et al, 1991] and death [Harrison et al, 1994; Krasna et al, 1988; Ouchi et al, 1996; Chapuis et al, 1985; Newland et al, 1994]. The presence of EMVI on a pre-operative MRI scan is associated with a four-fold higher risk of distant metastasis (52% vs. 12%), and a drop in relapse-free survival at 3 years to only 35% vs. 74% for patients with no EMVI [Newland et al, 1994].
By definition, histologically defined EMVI has to be associated with tumors that are at least stage T3.

The typical appearances on MRI, which is the only imaging modality that has been shown to consistently demonstrate EMVI in rectal cancer [Brown et al, 2003a], include the following four components:

- Pattern of tumor margin
- Location of tumor relative to major vessels
- Caliber of vessel
- Vessel border

The tumor margin may appear nodular or smooth. Tumor invasion into the small non characterizable veins that radiate outward from the bowel wall creates a nodular border. This finding can be differentiated from desmoplasia, which normally appears as fine stranding. Whenever a tumor is seen close to a vessel, the possibility of EMVI should be considered. The presence of tumoral signal intensity within a vascular structure is highly suggestive of EMVI. As a tumor invades along the lumen, the vessel expands, and the tumor may eventually expand through and beyond the vessel wall, disrupting the border, which can be described either as irregular or nodular [Smith et al, 2008] (Figure II.13).

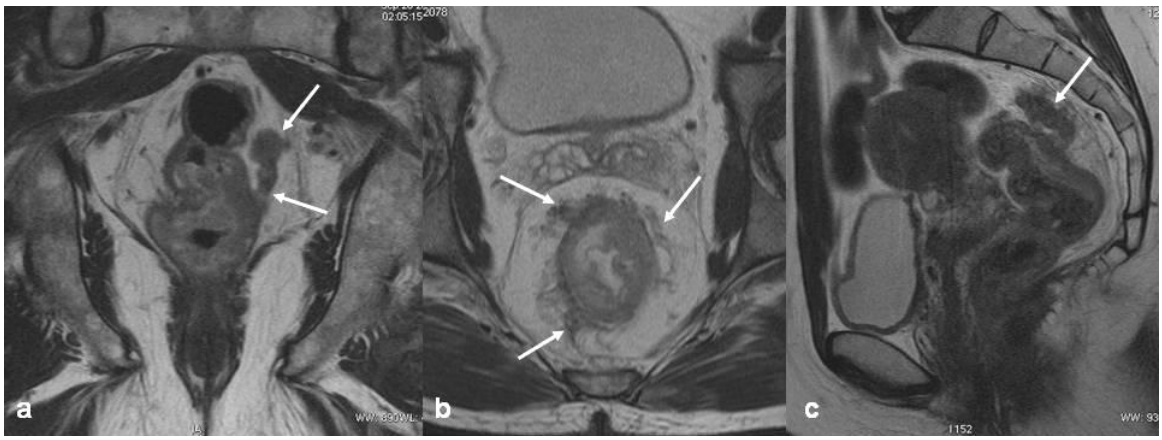


Figure II.13. Axial T2-weighted MR images of three patients with rectal cancer. There is tumoral signal intensity within vascular structures, associated with expansion of the vessel lumen (white arrows). In (b), the tumor margin appears nodular, as there is invasion into the small veins that radiate outward from the rectal wall.

The sensitivity and specificity of MRI for detecting EMVI has been reported to be around 62% and 88% respectively [Smith et al, 2008]. Some patients with microscopic vascular invasion could not be resolved on MRI, while others with very obvious EMVI on the pre-operative images had false-negative histopathology due to obliteration of normal venous architecture which makes it difficult for the pathologist to recognize that a certain tumor deposit lies within the course of a vessel, which may be more readily appreciated on serial MR images.

2.5. Peritoneal involvement

In rectal cancer, peritoneal involvement predicts for local recurrence [Smith and Brown, 2007].

The typical appearance on MRI is one of a nodular extension of intermediate signal intensity through the fine low-signal-intensity peritoneal reflection at or above the level of its attachment to the anterior surface of the rectum, best demonstrated on axial images (Figure II.14).

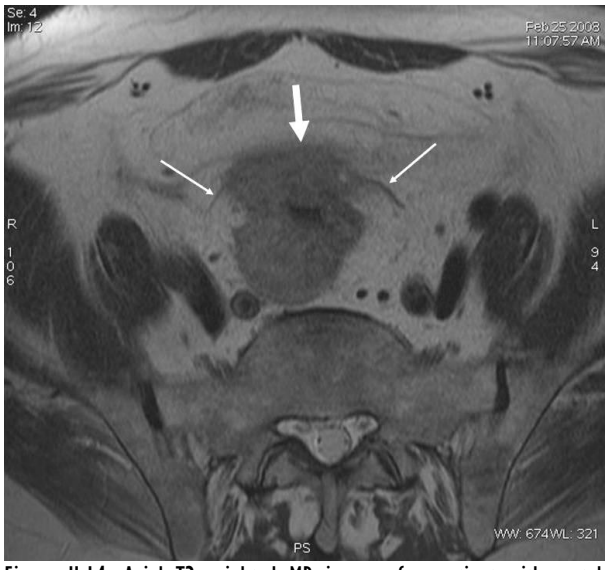


Figure II.14. Axial T2-weighted MR image of a patient with rectal cancer, displaying a nodular extension of intermediate signal intensity (thick arrow) through the fine low-signal-intensity peritoneal reflection (thin arrows) above the level of its attachment to the anterior surface of the rectum.

Although cases of peritoneal perforation were undoubtedly identified using preoperative MRI, many cases will be missed by MRI due to failure to resolve microscopic infiltration of peritoneal lined clefts [Smith and Brown, 2007].
The accuracy of MRI in correctly identifying peritoneal involvement at this site is therefore less reliable than detection of other prognostic factors [Brown and Daniels, 2005]. However, knowledge of the relationship of the tumor to the peritoneal reflection anteriorly should prompt a careful search for subtle peritoneal infiltration.

3. ASSESSMENT OF THERAPY RESPONSE

The objective of neoadjuvant therapy is to downstage and downsize the tumor in order to improve resectability and achieve better local control [Sauer et al, 2004; Reerink et al, 2003]. Tumor downstaging may lead to complete clinical response or pCR (pT0N0M0). These situations may occur in 10% to 30% of patients treated by neoadjuvant CRT and may be referred as stage 0 disease [Grann et al, 1997; Habr-Gama et al, 1998; Hiotis et al, 2002; Janjan et al, 1999; Luna-Perez et al, 2001; Medich et al, 2001].

3.1. MRF clearance

MRF involvement may be even more important in the post-neoadjuvant therapy setting than in the primary evaluation of rectal cancers. In advanced tumors with a positive margin on preoperative imaging, the prognosis is better if the margin becomes free after treatment. In

contrast, if the margin remains positive, the prognosis is worse than in cases without neoadjuvant therapy, because the remaining tumor consists of a selected population of tumor cells which are resistant to therapy [Nagtegaal and Quirke, 2008] (Figure II.15).

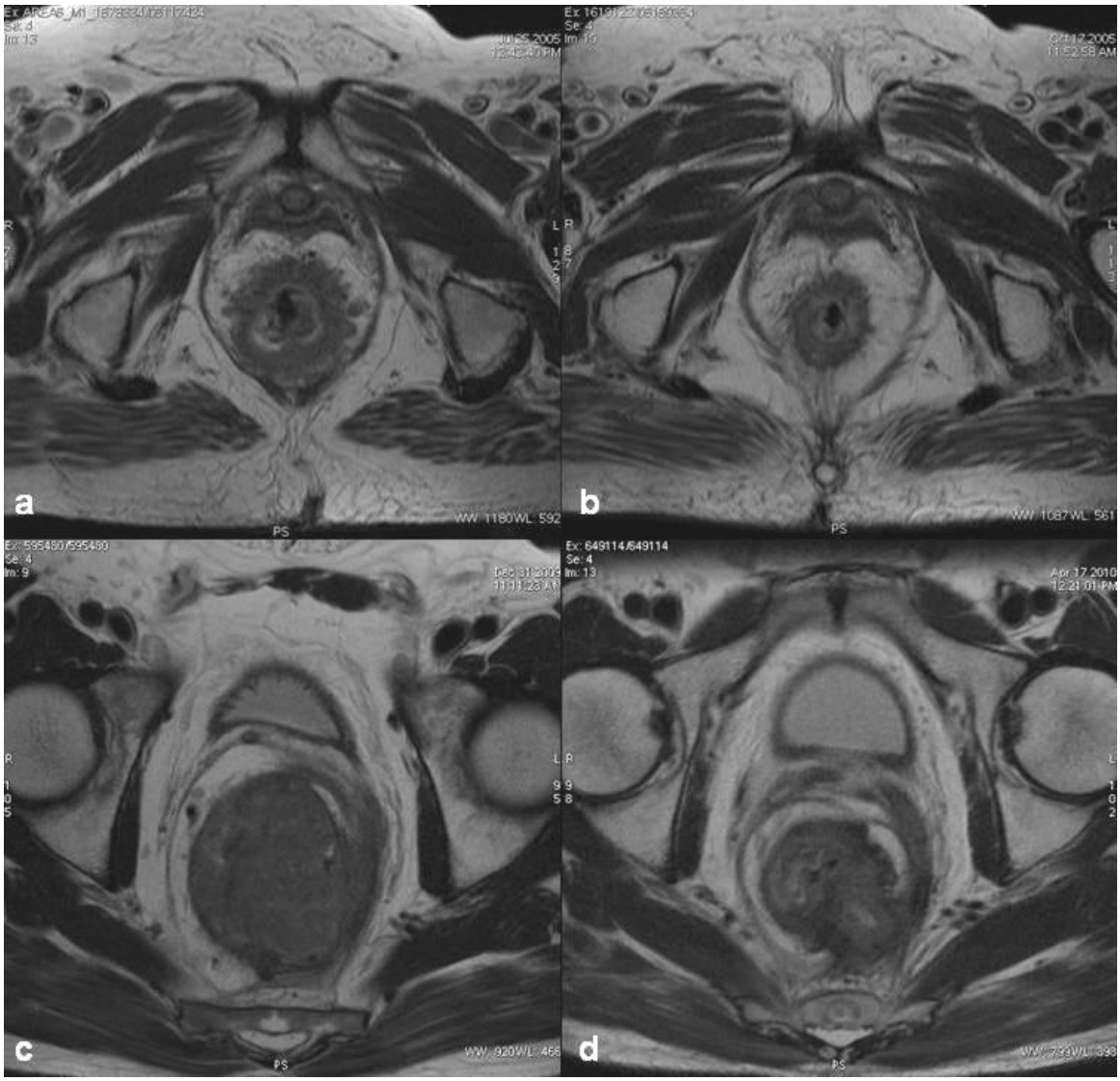


Figure II.15. Axial T2-weighted MR images of two patients with rectal cancer before CRT (a, c) and after completion of CRT (b, d). Before CRT, both lesions show an intimate contact with the MRF. However, after completion of CRT, despite the presence of downsizing for both lesions, on (b), a fat pad between the outer border of the tumor and the MRF develops, whereas on (d), there are still signs of MRF invasion. Both are ypT3tumors, but the prognosis is significantly better for the former, as the MRF became unthreatened after CRT.

Vliegen et al [2008b] reported an AUC for post-CRT MRI for assessing MRF/CRM invasion on the basis of morphologic criteria alone of 0.81 and 0.82 and a high sensitivity and NPV (both 100%) for two observers. However, their results showed only a moderate specificity (32% and 59%) and PPV (57% and 68%). The main challenge of post-CRT MRI in the judgment of MRF/CRM tumor invasion is the assessment of diffuse hypointense "fibrotic" tissue in the initial tumor area, which was seen in more than 50% of patients in whom this fibrotic tissue at MRI showed tumor infiltration at histological examination. Residual tumor within these fibrotic areas is often restricted to small tumor nests that are beyond the resolution threshold of MRI

[Dworak et al, 1997; Beets-Tan et al, 2000]. It is therefore virtually impossible based on morphological criteria alone to differentiate these from completely tumor-free areas of fibrosis.
Despite the problems of MRI in the interpretation of post-RT fibrosis, the same authors proved that the presence of diffuse iso or hyperintense tissue infiltration of the MRF on MRI was associated with tumor invasion at histological examination in 90% of the quadrants in which this pattern was seen [Vliegen et al, 2008b].
Recently, a Korean group [Park et al, 2011] evaluated the added value of DWI in combination with T2-w MRI compared with T2-w imaging alone for predicting tumor clearance of the MRF after neoadjuvant CRT in patients with locally advanced rectal cancer. The study included 45 patients and key results showed that the diagnostic performance regarding prediction of tumor clearance of the MRF for two observers improved significantly after additional review of DW images: AUC improved from 0.770 to 0.918 ($P = 0.017$) for observer 1 and from 0.847 to 0.960 for observer 2 ($P = 0.026$). Diagnostic accuracy (observer 1, $P < 0.001$; observer 2, $P = 0.022$), sensitivity (observer 1, $P < 0.001$; observer 2, $P = 0.002$), and NPV (observer 1, $P = 0.013$; observer 2, $P = 0.025$) were significantly higher when both DW and T2-w images were evaluated than when T2-w images alone were reviewed for both observers. Most overstaged cases on T2-w images (82%) were attributed to iso- or hyperintense masses abutting the MRF, corresponding to inflammation, fibrosis, or abundant mucin components at histological examination. Understaging of tumor clearance was due to microscopic tumor cell infiltration into the MRF despite fat pads larger than 2 mm between the area of viable tumor signal intensity and the MRF at MRI.
Tumor invasion within the MRF appears hyperintense at DWI and hypointense on ADC maps because of the diffusion restriction of the motion of protons. Therefore, these DWI features can help differentiate neoplastic from non-neoplastic lesions such as radiation-induced fibrosis and inflammation within the MRF, thus potentially improving the overall diagnostic accuracy of the prediction of MRF clearance after CRT in patients with rectal cancer. When DW images are used in combination with T2-w images, these serve as an anatomic reference for tumor location, which in turn leads to a more accurate assessment of the distance between viable tumor and the MRF, in spite of the comparatively low spatial resolution of DW images alone.

3.2. T and N downstaging

After CRT, Allen et al [2007] found that tumor downstaging occurred in 17% of cases, while nodal downstaging occurred in 68% of the patients.
The reported overall accuracy of MRI in assessing the pathologic stage of irradiated rectal cancer is 47%–54% (50%) for T staging and 64%–68% (65%) for N staging [Kuo et al, 2005; Chen et al, 2005; Vliegen et al, 2008b; Allen et al, 2007].
The relatively low accuracy of MRI in predicting the pathologic stage of irradiated rectal cancer seems to be associated to both overstaging and understaging. The major MRI finding that causes overstaging is diffuse hypointense tissue infiltration into the mesorectal fat. This is related to two histopathologic phenomena: marked fibrosis of the bowel wall and peritumoral infiltration with inflammatory cells and vascular proliferation (desmoplastic reaction). Most of the inaccuracy is associated with overstaging of pathologic stage T1 and T2 tumors [Kuo et al 2005; Chen et al, 2005; Valentini et al, 1998]. Also, radiation proctitis or ulceration can sometimes cause overstaging, so it is important to carefully compare post-CRT images with the pre-CRT images.

The most important cause of understaging is nonvisualization of the tumor mass on MRI. Changes in the rectum after CRT—such as histopathological alterations in the tumor, replacement by fibrotic scar tissue, and an island of residual adenocarcinoma—can make it difficult to identify viable tumor on MR images [Kuo et al, 2005, Chen et al, 2005, Valentini et al, 1998].

Understaging with MRI after CRT is not a problem in cases where curative surgery is to be performed; however, it is a dilemma when a change in the surgical strategy is considered for some patients, especially those experiencing a complete tumor response.

In patients in whom CRT has led to downstaging of tumors to lesions confined to the rectal wall (ypT0–2 tumors) and in whom there are no longer involved lymph nodes (ypN0 lesions), local transanal full-thickness excision of the bowel wall may be sufficient to achieve cure. Thus, the major challenge for the radiologist is to be able to recognize those tumors that, after CRT, are most appropriate for local excision – tumors confined to the rectal wall (Figure II.16).

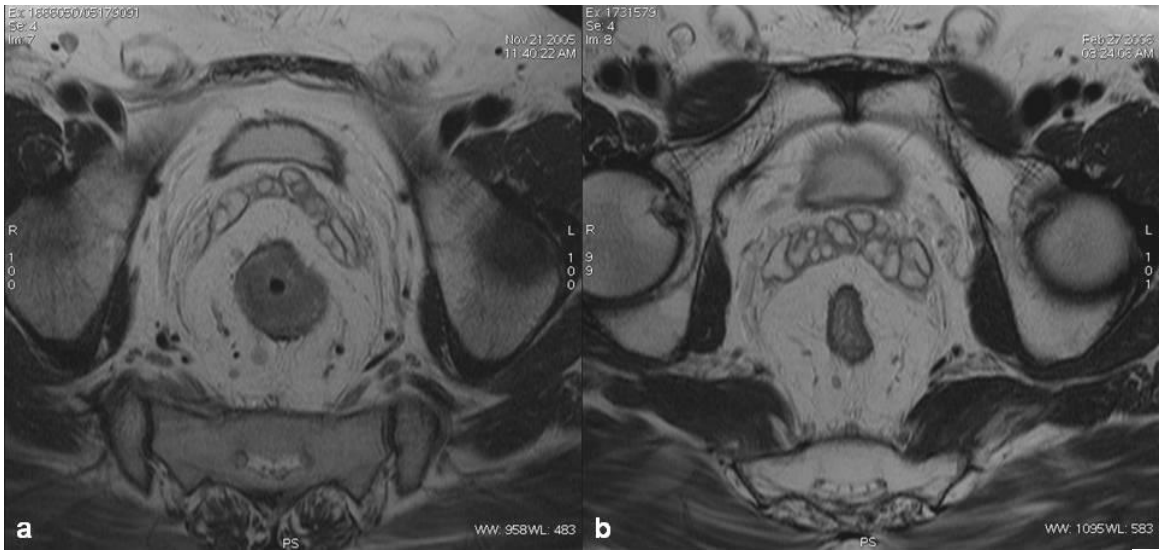


Figure II.16. Axial T2-weighted MR images of a patient with rectal cancer before CRT (a) and after completion of CRT (b). The reappearance of an intact hypointense muscular layer after CRT is indicative of a tumor limited to the rectal wall (ypT2).

In this regard, a previous study [Dresen et al, 2009] included 67 patients who underwent radiation therapy with concomitant chemotherapy and surgery. Results showed a PPV for prediction of tumor confined to rectal wall (ypT0–2) ranging from 86% to 91% on the basis of morphological criteria alone. The visualization of an intact hypointense bowel wall on T2-w MR images was highly predictive of a tumor limited to the bowel wall, explaining the high PPV.

However, when this appearance of the rectal wall could not be delineated, as for example when it has thickened owing to RT, fibrosis was suggested. The interpretation of fibrosis with or without residual tumor on MR images remains a challenge, also reported by other authors [Allen et al, 2007; Chen et al, 2005; Kuo et al, 2005; Hoffmann et al, 2002; Kahn et al, 1997; Kim et al, 2005; Maretto et al, 2007; Muthusamy and Chang, 2007]. Because of the presence of fibrosis, many ypT2 tumors were overstaged, and this factor was the cause of a low NPV as well as of a low sensitivity (which ranged from 25% to 42%) (Figure II.17).

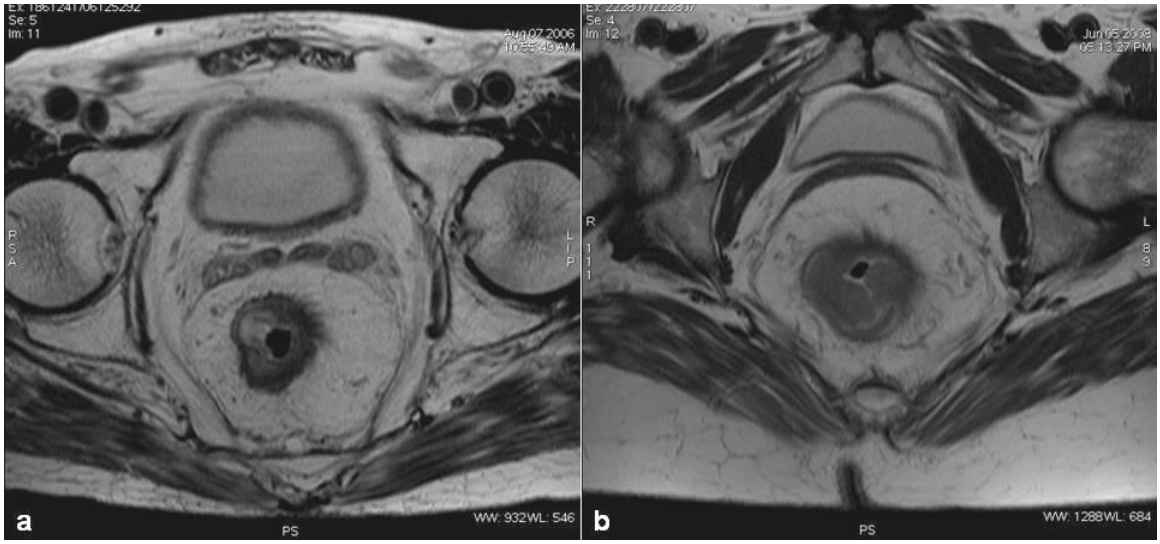


Figure II.17. Axial T2-weighted MR images of two patients with rectal cancer after CRT. Both demonstrate hypointense areas corresponding to fibrosis, as well as irregular borders with thin spiculations extending to the mesorectal fat. MRI cannot differentiate between purely fibrotic spiculations in a tumor confined to the rectal wall (a, ypT2) and spiculations containing microscopic foci of tumor (b, ypT3). As a result, many lesions similar to (a) are overstaged.

In the same study, the authors showed that ypT0–2 tumors had significantly smaller volumes than did ypT3–4 tumors before radiation therapy with concomitant chemotherapy (55 vs. 92 cm^3, $P = 0.038$). Volume reduction rates were significantly higher in ypT0–2 than in ypT3–4 tumors (89% vs. 61%, $P < 0.001$). If volume before CRT was 50 cm^3 or smaller and volume reduction rate was 75% or higher, the excised tumor was shown to be always confined to rectal wall (ypT0–2). By using these criteria, 43% of overstaged cases could have been correctly assigned as tumors confined to the bowel wall. Furthermore, when combined with morphological criteria, the PPV was very high (94%). While these tumors might be treated less extensively, in tumors with a volume reduction of less than one-third, the whole initial tumor area should be resected with standard TME, and, when necessary, the surrounding organs should be resected as well, because all these tumors remained as T3–4 tumors [Dresen et al, 2009].

After CRT, erradication of tumor in involved lymph nodes also occurs, with a reported decline in the rate of tumors with malignant lymph nodes found at histopathologic evaluation from 40% before CRT to 25% after it [Govindarajan et al, 2006; Reerink et al, 2003; Lehnert et al, 2002; Sauer et al, 2004]. Although a good response in the primary tumor generally is accepted to correspond with a good response in the lymph nodes, there are some conflicting findings, with reported rates of involved nodes ranging from 1.7% to 17% in patients with a complete response of the primary tumor [Hughes et al, 2006; Coco et al, 2007]. Only few reports on the accuracy of MRI to detect lymph node disease after CRT on a patient-by-patient basis have been published, with accuracy rates of 65%–88% and sensitivity and specificity varying from 33% to 82% and from 68% to 95%, respectively [Chen et al, 2005; Maretto et al, 2007; Suppiah et al, 2009; Koh et al, 2008].

In a study evaluating 201 histologically-matched lymph nodes, Lahaye et al [2009b] found that conventional T2-w MR images yielded an AUC for the short- and long-axis diameters of the nodes of 0.87 and 0.88 for observer 1 and 0.89 and 0.87 for observer 2, respectively. The optimal cutoff value of the short-axis diameter was 3.3 mm, with corresponding sensitivity and specificity for the detection of malignant nodes of 85% and 78%, respectively. The optimal cutoff value of the long-axis diameter was 4.8 mm, with corresponding sensitivity and specificity for the detection of malignant nodes of 82% and 82%, respectively [Lahaye et al, 2009b].

In a recent report, Lambregts et al [2011a] found an AUC of 88% for nodal characterization after CRT using standard MRI. A possible explanation for the good nodal staging results on MRI after CRT is that many irradiated nodes disappear, and of the remaining small nodes over 80% are sterilized [Koh et al, 2008]. Nodes that remain large after CRT are thus more likely to be malignant (Figure II.18).

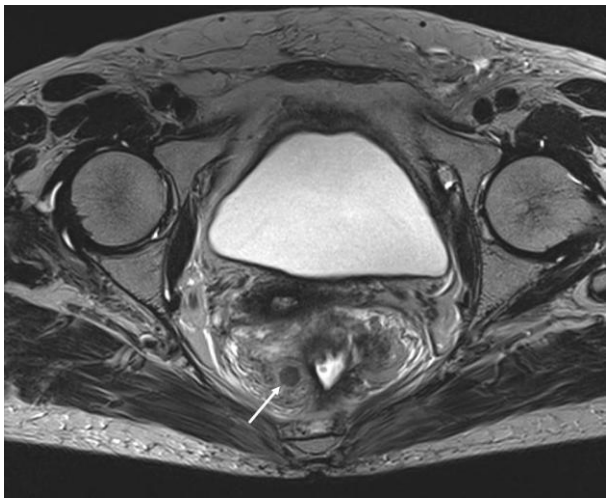


Figure II.18. Axial T2-weighted MR image of a patient with rectal cancer after CRT, displaying a large and slightly heterogeneous lymph node (white arrow). Histology of the surgical specimen confirmed its metastatic nature.

This allows a more reliable assessment of the nodal status on restaging MRI based on morphological criteria only [Lambregts et al, 2011a].

There are a number of observations that could explain the better performance of size criteria after CRT than in the primary staging setting. Small nodes often originate interpretation difficulties on standard T2-w fast spin-echo images, and after CRT, the number of lymph nodes harvested during histopathological evaluation drops by about 30% [Koh et al, 2008; Habr-Gama et al, 2008]. This could lead to fewer interpretation errors in small nodes, improving the accuracy. In addition, usually the lymph nodes that are still malignant after CRT are initially the larger nodes and small malignant nodes on primary staging often are benign after CRT [Lahaye et al, 2009b].

Regarding other imaging methods, in reports on nodal restaging with EUS and CT after CRT, investigators reached only moderate accuracy values of 0.61 and 0.62, respectively, which are comparable to those of primary nodal staging [Maretto et al, 2007].

Lahaye et al [2008] assessed the usefulness of USPIO-enhanced MRI for nodal restaging after CRT. They found that tumoral nodes that show no uptake of nanoparticles before CRT regain their capability for uptake of the USPIO contrast agent when the tumor is eradicated. This finding suggests that tumor cells are replaced by normal lymphoid tissue with macrophages, which are responsible for the uptake of nanoparticles of iron oxide [Harisinghani et al, 2002]. On a node-by-node analysis, USPIO-enhanced MRI yielded an AUC for the prediction of the nodal status of 0.99 for observer 1 and 0.98 for observer 2 on 3D T2*-w images. On a patient-by-patient basis, the sensitivity of USPIO-enhanced MR imaging for detection of malignant lymph nodes after CRT is close to 90%, with a specificity of 80% [Lahaye et al, 2008].

Lambregts et al [2011a] demonstrated a gain in accuracy in restaging lymph nodes with gadofosveset-enhanced MRI: the per lesion AUC improved from 0.88 on standard MRI to 0.94 on gadofosveset-MRI for reader 1 (P = 0.01) and from 0.87 to 0.95 for reader 2 (P = 0.04). On a

patient basis AUC changed from 0.75 to 0.79 for reader 1 (P = 0.54) and from 0.73 to 0.86 for reader 2 (P =0.06).

Recently, the same group published their work on the use of DWI-MRI in restaging mesorectal lymph nodes after CRT [Lambregts et al, 2011b]. Signal intensities did not differ between benign and metastatic nodes and rendered an AUC of 0.64 (95% CI 0.53–0.75) for reader 1 and 0.52 (95% CI 0.40–0.64) for reader 2. The AUC for detection of metastatic nodes was 0.66 using ADC values. The optimal ADC threshold was 1.25 $\times 10^{-3}$ mm^2/s, resulting in a sensitivity of 53%, specificity 82%, PPV 35% and NPV 91%.

The predicted probability for the combined assessment of T2w-MRI + ADC rendered an AUC of 0.91 for reader 1 and 0.96 for reader 2, which resulted in a sensitivity of 56%, specificity 98%, PPV 83% and NPV 92% for reader 1. These values were 56%, 99%, 95% and 93% for reader 2. The diagnostic performance when using ADC only was significantly lower than for T2w-MRI (P = 0.02 and P = 0.0003 for readers 1 and 2, respectively) and T2w-MRI + ADC combined (P = 0.001 and P < 0.0001). There was no significant difference in diagnostic performance between T2w-MRI and the combination of T2w + ADC (P = 0.17 and P = 0.26). ADC combined with standard T2w-MRI improved the diagnostic performance, however without accomplishing a significant improvement compared with T2w-MRI alone.

Again, these results suggest that after CRT, T2w-MRI alone is already satisfactory for nodal evaluation, reaching an AUC of 0.88–0.95. Such good results have also been reported by other groups, with high NPVs ranging between 81% and 100%, indicating that a restaging MRI after CRT can reliably recognize the ypN0 patients [Lahaye et al, 2009b; Suppiah et al, 2009]. Apparently, morphological criteria (size, shape and border) work better in a restaging setting. Many small (2–5 mm) nodes disappear after CRT, while up to 50% of these nodes initially harbored metastases [Dworak, 1989; Wang et al, 2005]. Interestingly, although it did not improve the overall performance, the addition of ADC to standard T2w-MRI did improve the PPV from 60–61% to 83–95%, thus reducing overstaging errors. The foremost advantage from the addition of DWI in this study was the higher number of detected nodes compared with conventional T2w-MRI. On DWI, high signal intensity nodes were more straightforwardly detected against the suppressed background signal of the neighboring tissues. DWI can thus be used to immediately focus a radiologist's eye on the presence of nodes and their location. When radiologists will become able to provide an imaging tool for the selection of patients with truly sterilized nodes, patients with a small tumor remnant limited to the rectal wall (ypT1-2N0) may be safely stratified for local excision, while patients with a complete response (ypT0N0) could be included in a wait-and-see policy with deferral from surgery [Lezoche et al, 2008; Borschitz et al, 2008; Habr-Gama et al, 2006].

Studies comparing the appearance on EUS and histopathology have shown that this imaging technique cannot reliably differentiate between fibrosis and tumor [Rau et al, 1999; Gavioli et al, 2000] and, hence, the degree of downstaging. In a study of 84 patients with locally advanced rectal cancer, EUS was performed 4 - 6 weeks after the completion of CRT [Rau et al, 1999]. The T stage was correctly determined in 15 of the 51 responders (29%) and in 27 of 33 non-responders (82%), whereas misinterpretation occurred in 36 of the responders (71%) and in 6 of the non-responders (18%) (P < 0.001). The distance of the tumor from the anal verge and tumor location on EUS did not correlate with the staging accuracy. Lymph node involvement was correctly assessed in 48 patients (57%) [Rau et al, 1999]. These findings supported previous data which showed an accuracy of only 47% in determining T stage [Napoleon et al, 1991].

Post-CRT EUS cannot visualize the MRF or the peritoneum and therefore is unable to determine their status. Therefore, EUS is not recommended for the assessment of patients after CRT or

RT because its sensitivity and specificity for the reassessment of the primary tumor are too unreliable [Evans et al, 2011].
Regarding PET, Calvo and colleagues [2004] showed a correlation of tumor downstaging with standard uptake value (SUV). In this study, tumors that were downstaged had a post-CRT maximum SUV of 1.9, compared with nondownstaged lesions that had a SUV of 3.3 (P = 0.03). Similarly, another study proved that all downstaged and downsized tumors showed a post-treatment low SUV (< 2.5) [Di Fabio et al, 2005]. Post-CRT SUV alone might be better than mean SUV reduction as a prognostic indicator [Oku et al, 2002].
Studies on the use of PET in restaging rectal cancer after CRT focused principally on the accuracy to detect complete responders or to evaluate the response, and data on the prediction of nodal status are scarce. In the prediction of the nodal status in primary rectal cancer, PET performs poorly, with a sensitivity of 21%–29%, and it is not presumed to perform much better after CRT [Abdel-Nabi et al, 1998; Llamas-Elvira et al, 2007], since in this setting the foci of tumor in malignant nodes are expected to be even smaller than in untreated rectal cancer, and the detection of small volumes of tumor is a well-known limitation of PET.

3.3. Complete response

The introduction of preoperative, rather than postoperative, CRT has led to a decline in local recurrence rates and has become standard of care for patients with locally advanced rectal cancer [Sauer et al, 2004].
If CRT is chosen for a patient with locally advanced rectal cancer, the patient is usually scheduled for an operation after completion of it. In 10–24% of patients, no residual tumor is found at histology after surgery [Maas et al, 2010].
These complete responders are known to have a very good prognosis, in terms of both overall and disease-free survival [Maas et al, 2010]. A complete response also raises the hotly debated and still controversial question of whether surgery is still necessary for these patients, particularly because TME may have associated morbidity and even mortality and has the potential risk of a permanent colostomy. Recently, a more conservative treatment was advocated in patients who showed a good or complete response to neoadjuvant treatment: in 2006, Habr-Gama et al [2006] presented the long-term results of a prospective trial that investigated a "wait-and-see" policy in a carefully selected group of patients with clinical and radiological evidence of a complete response after neoadjuvant CRT. Results at 5-year follow-up were favorable for the nonsurgical group, with an overall and disease-free survival of 93% and 85%, respectively [Habr-Gama et al, 2006].
However, in order to securely suggest such a deferral from surgery, it is essential to select accurately the correct candidates – the true complete responders.
The role of imaging for restaging after CRT has been the subject of a number of studies and all suggest that neither MRI nor EUS or PET are sufficiently accurate for identifying the true complete responders, with positive predictive values ranging from 17–50% [Janssen et al, 2010; Capirci et al, 2004; Kristiansen et al, 2008; Suppiah et al, 2009; Kim et al, 2009; Vanagunas et al, 2004].
In fact, when MRI is performed 4–6 weeks after the completion of preoperative CRT for locally advanced rectal cancer, it is seldom normal, even in patients who will demonstrate a pCR at surgery. Rather, in the majority of patients with an optimal response at MRI, a scar - represented

by a focal area of low-signal intensity on T2-w MR images - replaces the site of disease (Figure II.19).

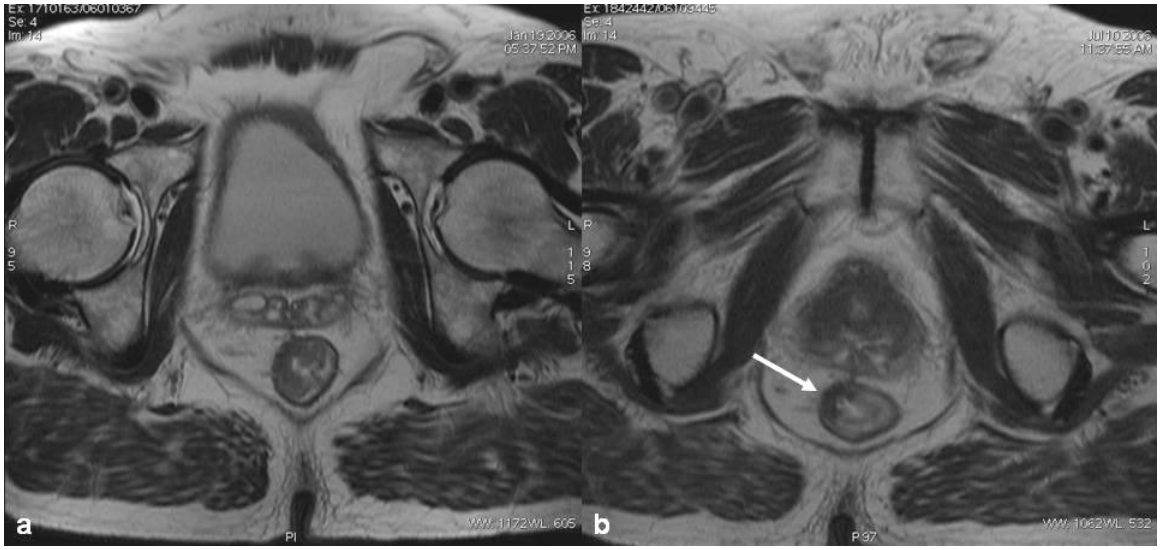


Figure II.19. Axial T2-weighted MR images of a patient with rectal cancer before CRT (a) and 8 weeks after completion of CRT (b). Before treatment there is a tumoral thickening extending over 50% of the rectal circumference. After CRT, the tumor has turned fully hypointense, which indicates a scar (white arrow).

The precise cellular composition of such an area of low signal intensity cannot be known, and a single MRI scan may not be able to diagnose complete response. In fact, the major component of error on MRI is overstaging due to its limited capability to allow differentiation between viable tumor, residual fibrotic non-tumor tissue, and desmoplastic reaction. [Kuo et al, 2005; Chen et al, 2005; Valentini et al, 1998] (Figure II.20).

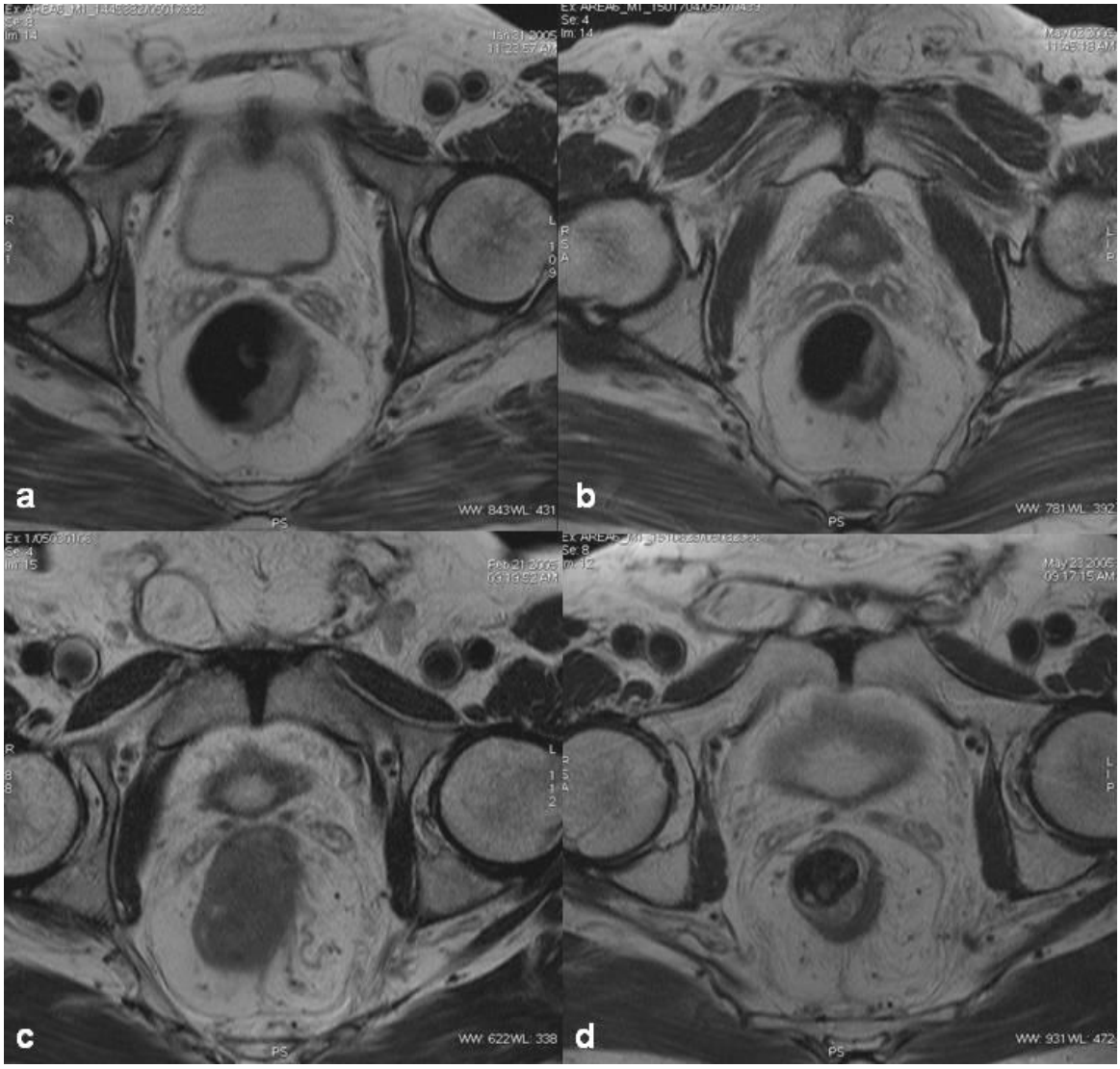


Figure II.20. Axial T2-weighted MR images of two patients with rectal cancer before CRT (a, c) and after completion of CRT (b, d). After CRT, both tumors suffer downsizing and become partially hypointense, with a very similar appearance. Morphological imaging cannot differentiate a complete response with only a fibrotic scar (b, ypT0), from fibrosis with viable tumor remnants within it (d, ypT3).

However, if surgery is deferred, then the scar can be followed with serial MRI examinations to monitor any change.

Due to the limitations of purely morphological MR images, recent attention has been directed toward DWI-MRI as a complement to standard morphological MRI for detection of complete responders, because on DWI viable tumor remnants are recognized as hyperintense foci compared with the low signal intensity of the surrounding nonneoplastic background tissue [Kim et al, 2009; Lambregts et al, 2011c] (Figure II.21).

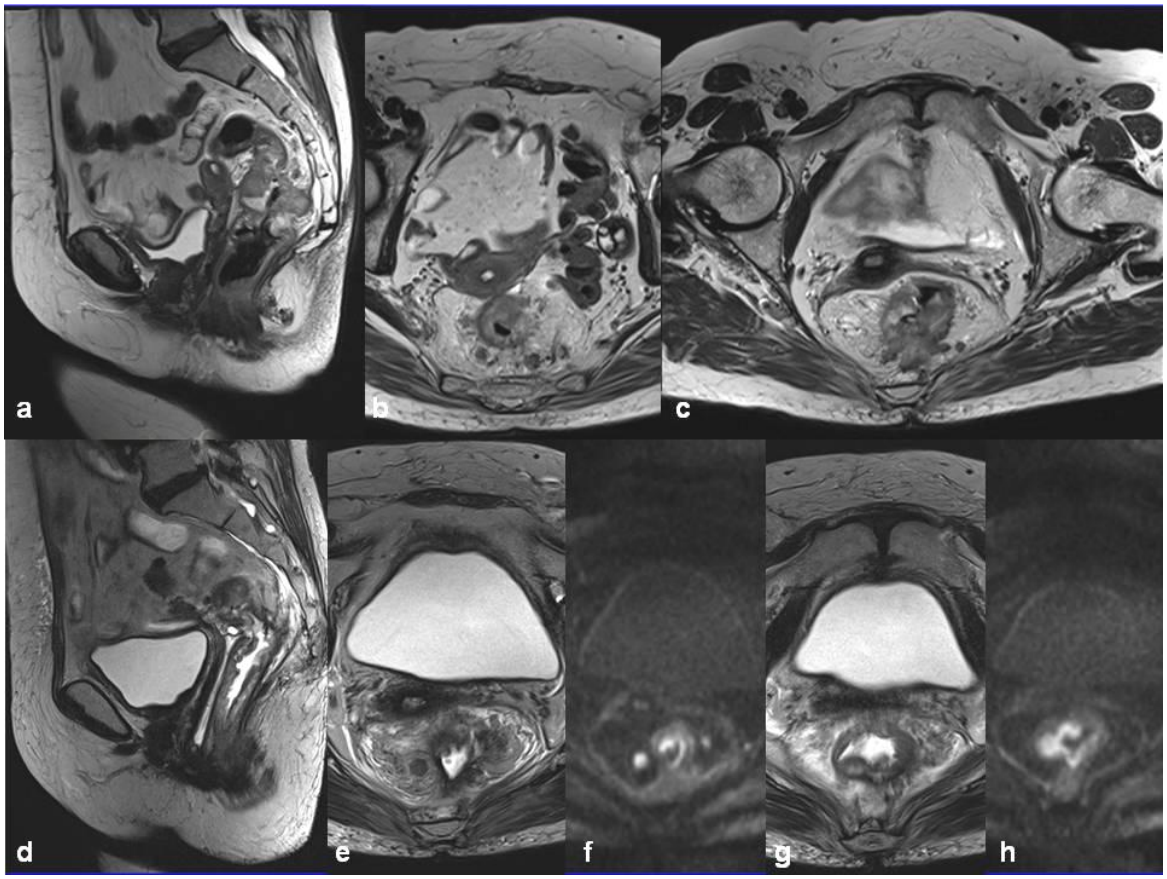


Figure II.21. Axial T2-weighted MR images of a patient with rectal cancer before CRT (a, b, c) and after completion of CRT (d, e, g) and axial high b-value DW images after CRT (f, h). Before treatment the tumor contacts the MRF and there are several large and heterogeneous lymph nodes in the mesorectum. After CRT, the tumor suffers downsizing and becomes mostly hypointense, corresponding to fibrosis, which precise composition could not be determined on purely morphological images. DWI clearly depicts hyperintense areas (of diffusion restriction), corresponding to zones where there are still viable tumor remnants. Additionally, a large lymph node, which was proved to be metastatic, remains after CRT (e), showing also diffusion restriction (f).

Kim et al [2009] showed in a study including 40 patients that DWI in addition to standard MRI significantly improved the performance of radiologists to select complete responders compared with standard MRI only.

A recent study by Lambregts et al [2011c], indicated that the diagnostic performance for predicting a pCR after CRT improved for the combination of standard MRI + DWI (AUC 0.78–0.8) compared with standard MRI only (AUC 0.58–0.76). Moreover, it resulted in a substantial decrease in the number of equivocal scores and an improved interobserver agreement.

The superior sensitivity for the combination of MRI + DWI resulted in less overestimation of residual tumor in patients with a pCR. This was true mainly because on the restaging MRI without DWI many interpretation difficulties were observed when the primary tumor bed had become 'fibrotic' as a result of the neoadjuvant treatment. In these cases, as mentioned previously, it becomes hard to differentiate small areas of residual tumor from simple fibrosis and readers tend to overestimate the presence of tumor [Barbaro et al, 2009; Kuo et al, 2005; Dresen et al; 2009, Jonas and Bahr, 2006]. In this particular setting, the functional information from DWI might be valuable: areas of fibrosis typically have low cellular density, which results in low signal intensity on high b-value diffusion images [Vandecaveye et al, 2007]. On the other hand, areas of residual tumor have a relatively high cellular density and show high signal on DWI, which is easily recognizable within the low signal of the surrounding tissue/fibrosis, thus allowing

a better depiction of small areas of residual tumor on DWI [Kim et al, 2009; Vandecaveye et al, 2007].
Specificity for MRI and DWI is > 90%, indicating that residual tumor is accurately detected and the risk for undertreatment will be < 10%. Although DWI allows detection of even small tumor volumes, the detection of microscopically small clusters of residual tumor cells, which are difficult to detect—even at histology— and are currently beyond the detection threshold of any available imaging modality (including DWI) will remain the major challenge for imaging.
Studies on the use of PET in restaging rectal cancer after CRT focusing on the accuracy to detect complete responders yielded a sensitivity to detect a pCR (in both the primary tumor and the lymph nodes) of 45%, with a specificity of 79% [Capirci et al, 2004; Kristiansen et al, 2008]. These results derive, at least partially, from the fact that initially following the completion of CRT, an increased tracer uptake may be caused by inflammatory changes and not always associated with residual tumor [Haberkorn et al, 1991; Engenhart et al, 1992; Moore et al, 2003].

3.4. Prediction of therapy response before and during CRT

One of the most remarkable findings associated with the use of DWI in patients with cancer has been that ADC measurements appear to be predictive of tumor response to CRT.
Studies in rectal cancer have shown that tumors with low baseline pre-treatment ADC values responded better to chemotherapy or RT than neoplasms that exhibited high pre-treatment ADC values [DeVries et al. 2003; Dzik-Jurasz et al. 2002]. Sun and co-investigators [2010] observed that the mean pre-CRT ADC value ($1.07\pm0.13\times10^{-3}$ mm^2/s) in the group of tumors that showed T-downstaging (17 out of 37 patients) was lower than that ($1.19\pm0.15\times10^{-3}$ mm^2/s) in the T-non-downstaged group ($P = 0.013$). One possible explanation is that tumors with high pre-treatment ADC values are likely to exibit more necrotic areas than those with low values [Koh and Collins, 2007]. Necrotic tumors are frequently hypoxic, acidic, and poorly perfused, which leads to reduced sensitivity to chemotherapy and RT.
However, other studies have failed to replicate those results. Kim and collaborators [2011] could not reliably discriminate pCR from non-pCR based on the pre-CRT ADC, and Heo and co-authors [2010] also reported that the pre-CRT ADC value was not significantly correlated with TRG after the analysis of 39 patients.
These differences may be attributable, at least partially, to the distinct definitions of response: some authors used the tumor size (50% reduction) as a criterion [Dzik-Jurasz et al, 2002], while others predefined responders as the T-downstaged group [Sun et al, 2010] and others considered pCR as the endpoint for response [Kim et al, 2011].
A recent study by Sun et al [2010] showed that at the end of the 1st week of CRT, the mean tumor ADC increased significantly from $1.07\text{x } 10^{-3}$ mm^2 /s to $1.32 \text{ x } 10^{-3}$ mm^2 /s ($F = 37.63$, $P < 0.001$) in the downstaged group, but there was no significant ADC increase in the non-downstaged group ($F = 1.18$, $P = 0.291$). It is believed that increases in ADC are a consequence of cellular damage leading to necrosis [Chenevert et al, 1997; Thoeny et al, 2005]. Another reason for the increase in ADC seen within 1 week is tumor edema caused by the massive release of VEGF within hours of even the first fraction of RT. That would lead to increased vascular permeability and increased interstitial volume, which would in turn increase ADC [Sun et al, 2010]. The mean percentage of tumor ADC change in the downstaged group was significantly higher than that in the non-downstaged group at each time point ($F = 18.39$, $P <$

0.001). This phenomenon may be explained by a higher degree of cellular necrosis achieved with CRT in the downstaged group than in the non-downstaged group. So, the difference of increase of the ADC after the beginning of CRT reflected mainly the different sensitivity of the tumor cells to CRT in the two groups [Sun et al, 2010]. In this way, these authors suggest that early temporal changes in ADC and pre-therapy ADC can potentially discriminate patients with locally advanced rectal cancers that are resistant to pre-operative CRT, which may allow a prompt modification of the treatment protocols [Sun et al, 2010].

Dynamic contrast-enhanced (DCE)-MRI studies have been performed most commonly for evaluating the effects of novel therapies such as antiangiogenic agents that affect blood vessels, usually in the setting of clinical drug trials [Morgan et al, 2003].

Signal enhancement seen on T1-w DCE-MRI sequences can be assessed semiquantitatively by analyzing signal intensity changes or quantitatively by pharmacokinetic modeling of contrast agent concentration changes.

The most commonly used model for analyzing DCE-MRI data uses two compartments where the contrast agent resides (blood plasma and extravascular–extracellular space). The volume transfer constant between the blood plasma and the extravascular–extracellular space, the wash-in rate (K^{trans}, measured in $minutes^{-1}$) and the rate constant between the extravascular–extracellular space back to the blood plasma, the wash-out rate (k_{ep}, measured in $minutes^{-1}$) determine the transport between these two compartments [Figueiras et al, 2010].

Physiologically, K^{trans} indicates a variable combination of the flow and permeability properties [Sessa et al, 2008]. For blood vessels where leakage is rapid (that is, when the extraction fraction during the first pass of the contrast agent is high, as typically is found in tumors), perfusion will determine contrast agent distribution and K^{trans} approximates to tissue blood flow per unit volume. There are circumstances in which transport out of the vasculature does not significantly deplete intravascular contrast medium concentration (that is, tissues with lower first-pass extraction fraction). This is typically found after treatment with chemotherapy or late after RT and in fibrotic lesions, and in these situations, K^{trans} approximates to the product of permeability and the surface area (permeability surface area product) [Figueiras et al, 2010].

There has been some work evaluating response to CRT of primary rectal cancer. Tumors with higher K^{trans} values at presentation appear to respond better to CRT than those with lower values. After CRT, K^{trans} values in general are lower, with persistent high values indicating residual active disease [George et al, 2001].

PET has also been used to predict response to CRT. For example, Cascini et al [2006] described a group of 33 patients with locally advanced rectal cancer submitted to neoadjuvant CRT, in whom PET could predict pathologic response to preoperative treatment. All patients had PET at baseline and 12 days after starting chemoradiotherapy (interim PET). For all examinations, the percentage decrease in SUV mean and max was correlated with pathologic response classified as TRG. The study reports that interim PET is strictly correlated with final pathologic response, with better results compared with presurgical scan. In particular, ROC analysis showed that the decrease in SUV mean correctly distinguished responders from nonresponders with an accuracy of 100%, whereas the decrease in SUV max yielded an accuracy of 97%.

Janssen et al [2010] prospectively evaluated 30 patients referred for preoperative CRT who underwent sequential PET-CT imaging at four time points: prior to therapy, at day 8 and 15 during CRT, and shortly before surgery. Tumor metabolic treatment responses were correlated with the pathological responses by evaluation of the TRG and the pathological ypT stage of the resected specimen. They showed that the response index (RI) for the SUV max on day 15 was the best predictive factor for the pathological response (AUC = 0.87) compared to the RI on

day 8 (AUC = 0.78) or the RI of presurgical PET imaging (AUC = 0.66). A cutoff value of 43% for the reduction of SUV max resulted in a sensitivity of 77% and a specificity of 93%. As such, an accurate PET-based prediction of the pathological treatment response is feasible already after 2 weeks of CRT. This could help to select patients to be considered for less invasive surgical interventions or even a deferral from surgery. Similarly, early modifications of the treatment protocol are possible, which might result in an improved clinical outcome.

4. DETECTION OF RECURRENT DISEASE

Eighty percent of patients with colorectal cancer present with local disease amenable to surgery with curative intent [Jessup et al, 1997]. Of these, around 40% will develop recurrent cancer, mainly within the first 3 years after treatment [Abir et al, 2006; Arriola et al, 2006; Desch et al, 2005; Kraemer et al, 2001].

Pelvic recurrence remains a significant dilemma with rectal cancer, occurring in 3% to 47% of patients [Abulafi and Williams, 1994; Sagar and Pemberton, 1996; Titu et al, 2006].

Relapse after initial surgery of CRC is responsible not only for significant morbidity and mortality, but also for impaired quality of life [Beets-Tan and Beets, 2004; Camilleri-Brennan and Steele, 2001; Miller, 1998]. Only between 20% and 30% of patients with local relapse detected during follow-up have tumors that are deemed to be resectable at the time of diagnosis [Goldberg et al, 1998]. Aggressive surgical approaches for colorectal cancer recurrence confined to a single organ are associated with a 5-year survival rate of up to 30% in selected patient populations [Abir et al, 2006; Arriola et al, 2006; Huguier et al, 2001; Titu et al, 2006].

Local recurrence is defined as clinical, radiologic, and/or pathologic determination of rectal cancer recurrence in the prior pelvic treatment field [Guillem et al, 2005]. Local relapse can be further divided into extraluminal recurrence (in which tumor regrowth occurs in and around the tumor bed, including the perirectal fat and the lymph nodes) and intramural recurrence (in which the tumor regrowth involves the region of the bowel anastomosis) [Abulafi and Williams, 1994]. The majority of local recurrences originate within the tumor bed, which emphasizes the importance of visualization of the perirectal tissues as part of postoperative follow-up [Titu et al, 2006]. To augment the likelihood of cure it is therefore fundamental to diagnose local recurrences when still in an early stage. To guide salvage surgery, an anatomically correct description of the location and extent of relapse is essential.

In general, diagnostic imaging for postoperative surveillance of rectal cancer should have the potential to differentiate between scar and extraluminal recurrence, as well as to identify anastomotic recurrence. In addition to CEA monitoring and endoscopy, CT, MRI, and PET are used as diagnostic imaging modalities for the detection of local relapse of rectal cancer. Nevertheless, the role of diagnostic imaging for routine follow-up of rectal cancer patients remains controversial because no single strategy for postoperative surveillance has been unequivocally shown to improve survival or cure rate [Guillem et al, 2005; Giordano et al, 2006; Longo and Johnson, 2002]. Moreover, the alteration of the pelvic anatomy associated with previous surgery and CRT remains a diagnostic challenge for all imaging strategies in detecting recurrence.

As such, it is still unclear whether imaging is beneficial during the surveillance of patients after rectal cancer surgery [Desch et al, 2005; Schaefer et al, 2007; Glimelius et al, 2010, Titu et al, 2006] and trials to establish the role of imaging are ongoing. However, if during follow-up a patient is suspected of having a local recurrence based on clinical symptoms and/or rising CEA

levels, CT is usually the imaging investigation to be performed in order to confirm or rule out the presence of a local or distant relapse [Desch et al, 2005; Schaefer et al, 2007; Valentini et al, 2009]. A pelvic mass that enlarges on consecutive post-operative CT studies is highly suspicious for a local recurrence, although the diagnosis is not always easy to make [Takeuchi et al, 1999; Flamen et al, 1999].

However, few data exist elucidating the role of MD-CT for staging recurrent rectal cancer [Stueckle et al, 2005; Stueckle et al, 2006]. In a study with 83 patients, the sensitivity and specificity of MD-CT for diagnosing pelvic recurrence in the second postoperative examination was 82% and 97%, respectively, if multiplanar reconstructions were routinely performed [Stueckle et al, 2005].

On the contrary, a study by Blomqvist et al [1996] in which twenty-five patients were enrolled, showed that MRI was the most effective imaging modality, with an accuracy of 87.5% compared with CT, which correctly diagnosed recurrent cancer in 76%. In another comparative study, Pema et al [1994] analyzed the importance of CT and MRI in diagnosing recurrent rectal cancer. Eighteen patients were included in this small study: MRI was the superior imaging method with a sensitivity of 91%, a specificity of 100%, and an overall accuracy of 95%, while CT reached values of 82%, 50%, and 68%, respectively.

Sometimes the CT findings are equivocal and in those cases PET / PET-CT have proven beneficial in identifying local tumor re-growth [Flamen et al, 1999; Even-Sapir et al, 2004]. PET may help detecting pelvic recurrence in rectal cancer patients [Akhurst and Larson, 1999], with reported accuracies ranging from 74% to 96% [Schaefer and Langer, 2007]. In a retrospective study, Moore et al [2003] investigated the impact of PET for the detection of pelvic recurrence of 60 previously irradiated rectal cancer patients. This imaging technique correctly identified 16 of the 19 documented recurrences, with a sensitivity, specificity, overall accuracy, PPV, and NPV of 84%, 88%, 87%, 76% and 92%, respectively. Even-Sapir et al [2004] assessed the role of PET-CT in the detection of local recurrence of rectal cancer. Sixty-two patients underwent PET-CT examination, which was found to be more sensitive and specific than PET alone. PET-CT correctly depicted 23 of the 24 pelvic recurrences, and allowed to differentiate benign lesions from pre-sacral recurrences with a sensitivity of 100% and a specificity of 96%, despite a histological diagnosis being possible in only 30 of 81 analyzed lesions.

Unfortunately, PET still has some limitations. The detectability of tumor depends on tumor size and FDG uptake [Fukunaga et al, 2004], and as such PET cannot recognize small volume disease due to its well known limitation in spatial resolution of around 4 – 6 mm [von Schulthess et al, 2006]. PET has demonstrated low sensitivity for lymph node staging in rectal cancer [von Schulthess et al, 2006]. Mucinous adenocarcinomas display poor radiotracer uptake [Kamel et al, 2004]. Radiation-induced inflammation in the first 12 months after RT reduces specificity, whereas sensitivity is limited in patients receiving chemotherapy because tumor tissue might not be metabolically active [Moore et al, 2003]. Additionally, physiological uptake in other pelvic organs (bladder, small bowel loops, seminal vesicles, and uterus) is associated with false-positive interpretations [Even-Sapir et al, 2004]. Due to problems with costs and availability, some authors suggest that PET imaging should be reserved for patients with increasing CEA levels and an otherwise normal diagnostic work-up [Abir et al, 2006].

As mentioned above in some studies comparing it to CT in this setting, MRI has proven to be helpful for assessing the resectability of a diagnosed local recurrence of rectal cancer [Dresen et al, 2010], and it is thought to be one of the leading imaging modalities for detection of a pelvic recurrence of rectal cancer [Stoker et al, 2000; Markus et al, 1997; Torricelli et al, 2003; Dicle et al, 1999], due to its excellent soft-tissue resolution and detailed anatomic information. The

distinction of recurrent cancer within a pre-sacral scar is more accurate compared with CT, based on differences in signal intensity between tumor and fibrosis [Dicle et al, 1999]. The main problem for MRI is the detection of a small growing tumor in an area of fibrotic scar tissue [Dresen et al, 2009; Kuo et al, 2005; Barbaro et al, 2010].
DWI-MRI is a promising technique for the detection of small tumor volumes whose benefit has been shown also in pelvic tumors [Koh and Collins, 2007; Namimoto et al, 2009; Rao et al, 2008]. As an addition to standard anatomical MRI, DWI could increase the diagnostic performance for detection of locorregional tumor recurrences [Nishie et al, 2008] (Figure II.22).

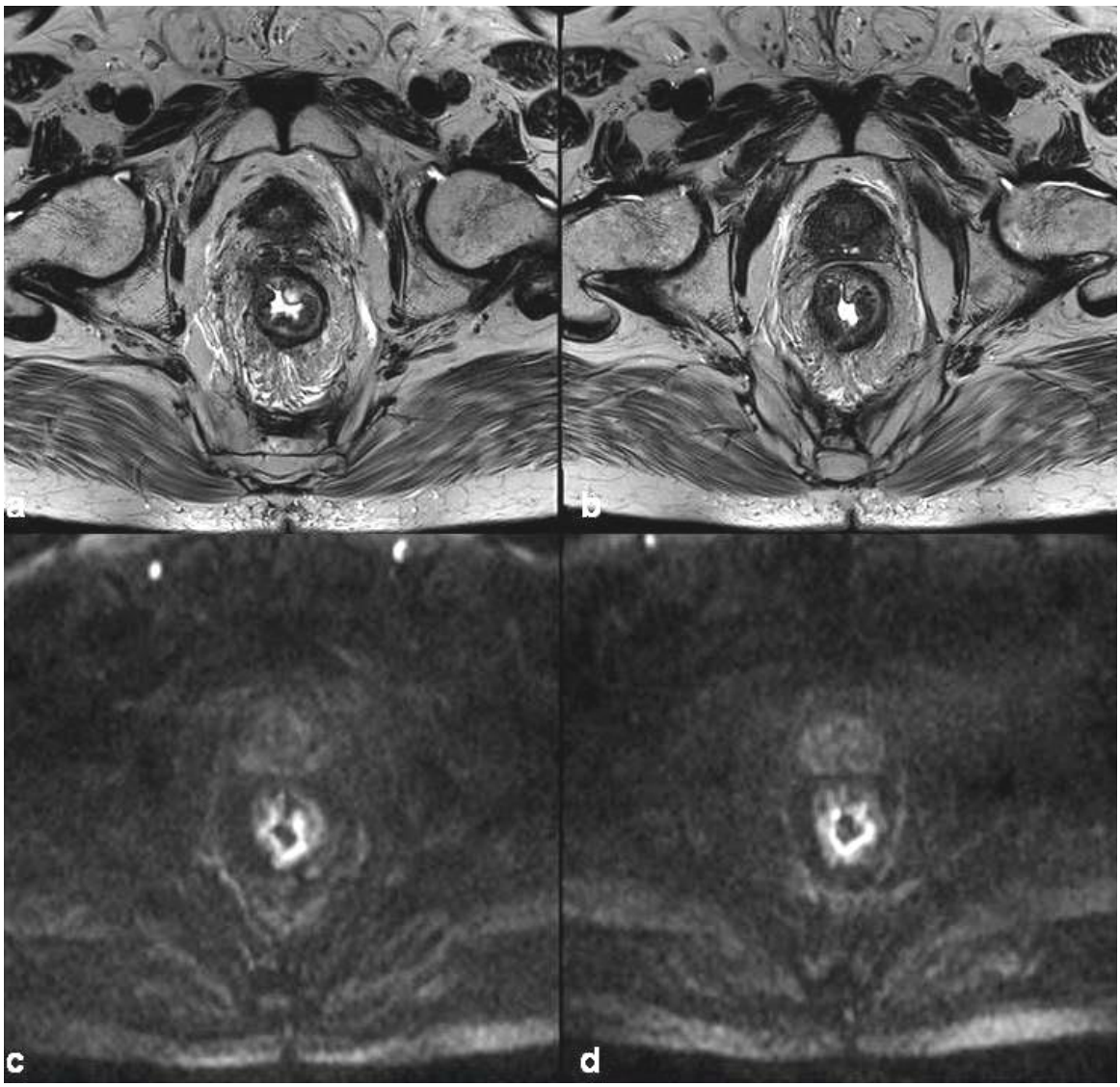


Figure II.22. Axial T2-weighted (a, b) and, b1000 DW (c, d) images of a patient who had previously undergone rectal surgery. On T2-weighted MRI (a, b) there is an area of intermediate signal intensity within the rectal wall. On DWI (c, d), there is an area of high signal intensity corresponding to viable tumor, confirming the intramural recurrence, which was histologically proven after surgical excision.

Lambregts et al [2011d] evaluated the accuracy of standard MRI, DWI and fusion images for the diagnosis of locally recurrent rectal cancer in patients with a clinical suspicion of recurrence. Two readers evaluated the images: reader 1 achieved an AUC of 0.99, sensitivity 100% and specificity 83% on standard MRI versus 0.98, 100% and 91% after addition of DWI (P = 0.78). For

reader 2 these values were 0.87, 84% and 74% on standard MRI and 0.91, 89% and 83% with DWI (P = 0.09). Fusion images did not significantly improve the performance. Interobserver agreement was κ=0.69 for standard MRI, κ=0.82 for standard MRI + DWI and κ=0.84 for the fusion images. The benefit of DWI was considered to be potentially more important for the detection of smaller tumors which are more difficult to detect within the fibrotic scar tissue. Other authors also showed that mainly anastomotic recurrences—which tend to be smaller in size—are missed with imaging, again suggesting that the benefit from additional functional imaging may be higher in the detection of these small tumors [Syk et al, 2008]. Interestingly, adding DWI to conventional imaging improved the interobserver agreement and reduced the number of false positives. DWI thus seems to increase the confidence of radiologists in ruling out the presence of a recurrence.

Prior studies demonstrated that standard MRI generally tends to overestimate the presence of tumor within areas of fibrotic postoperative scar tissue [Dresen et al, 2009; Kuo et al, 2005; Barbaro et al, 2010; De Lange et al, 1989]. When the signal intensities of areas suspected for local tumor recurrence on T2-w MRI were analysed, authors reported equally low signal intensities for areas of desmoplastic reaction containing tumor and areas of desmoplasia only [De Lange et al, 1989]. Also in these cases, the combination of the morphological information from MRI and the functional information from DWI can be beneficial in the diagnosis of recurrent tumor. Fibrotic areas typically possess low cellular density and a large interstitial space, which results in low signal intensity on high b-value DW images. Conversely, tumoral tissue has a relatively high cellular density, which will result in high signal on DWI [Vandecaveye et al, 2007].

Some authors have suggested the use of DCE-MRI sequences for a better diagnosis of recurrent tumor [Kinkel et al, 1996; Torricelli et al, 2003]. However, their value is somewhat conflicting as other reports have shown little improvement for DCE-MRI in comparison to standard morphological MRI [Blomqvist et al, 1998].

PART II

Personal contribution

Chapter III

Clinical study: Diffusion-weighted magnetic resonance imaging in rectal cancer: apparent diffusion coefficient as a potential non-invasive marker of tumor aggressiveness

1. INTRODUCTION

The prognosis of rectal cancer depends on several factors, some of which are traditionally assessed by histopathological examination of the surgical specimen. These include the degree of tumor invasion into and beyond the bowel wall [Jass and Love, 1989; Willett et al, 1999], the number of lymph nodes involved by tumor [Wolmark et al, 1986; Tang et al, 1995], and involvement of the mesorectal fascia (MRF) [Adam et al, 1994], which can also be assessed pre-operatively by magnetic resonance imaging (MRI) (Beets-Tan et al. 2001a, Brown et al. 2003a). Other factors with proven prognostic importance include the plasmatic level of carcinoembryonic antigen (CEA) as well as histological factors such as the tumor differentiation grade or the presence of lymphangiovascular invasion (LVI) [Huh et al, 2010; Gu et al, 2010; Du et al, 2009].

The current trends in the management of rectal cancer point towards a more widespread acceptance of neoadjuvant therapies. These create an increasing need for preoperative imaging methods to non-invasively select high-risk patients who could benefit from the more aggressive multimodality treatment approaches [Barrett, 1998; Colorectal Cancer Collaborative Group, 2001]. Detailed information on the patient's individual tumor profile should allow optimization of therapy and is also relevant in terms of prognosis, by providing a way to determine the risk for local and distant recurrence [Kremser et al, 2003].At present, the use of diffusion-weighted imaging (DWI) incorporated into a standard MR protocol is gradually increasing because of its proven benefit not only for tumor detection/characterization but also for monitoring treatment response [Koh and Padhani, 2006; Koh and Collins, 2007; Patterson et al, 2008; Padhani et al, 2009]. Diffusion-weighted imaging measures water diffusion characteristics, which are dependent on multiple factors such as cell density, vascularity, viscosity of extracellular fluid and cell membrane integrity [deSouza et al, 2008]. By quantifying these properties and expressing them as an apparent diffusion coefficient (ADC), DWI could potentially be used as an imaging biomarker to better select patients with poor prognosis who will truly benefit from a more aggressive neoadjuvant treatment [Lambrecht et al, 2010].

To date the value of ADC as a quantitative biomarker in patients with rectal cancer is not clear yet. Data are scarce and most published data on the value of DW-MRI for prediction of response to chemoradiation are conflicting [Kremser et al, 2003; Lambrecht et al, 2010; Kim et al, 2011; Sun et al, 2010; DeVries et al, 2003; Dzik-Jurasz et al, 2002]. We hypothesize that pre-treatment tumor ADC values may reflect the tumor profile of aggressiveness.

As the aggressiveness of rectal tumors is expressed by several factors, including T stage, N stage, involvement of the MRF, CEA levels, differentiation grade of the tumor and the presence of LVI,

[Jass and Love, 1989; Willett et al, 1999; Wolmark et al, 1986; Tang et al, 1995; Adam et al, 1994; Huh et al, 2010, Gu et al, 2010; Beets-Tan et al, 2001a; Brown et al, 2003a; Wieder et al, 2007; Ho et al, 2008; Lahaye et al, 2005] we aim to assess the value of DW-MRI as expressed by the quantified ADC values as a potential non-invasive imaging biomarker of tumor aggressiveness in rectal cancer.

2. MATERIALS AND METHODS

2.1. Patients

Between October 2007 and November 2010, 86 consecutive patients were considered for inclusion in this retrospective study. Inclusion criteria were 1) histologically (biopsy) proven rectal carcinoma, 2) treatment by surgical resection with or without neoadjuvant therapy, 3) availability of pathological reports of surgical specimens mentioning tumor differentiation grade, and 4) availability of primary staging MRI including DWI. Patients with mucinous appearing tumors on the primary staging MRI (completely hyperintense on T2-weighted images without any solid tumor parts) were excluded, since they are known to have low cellular density, exhibiting high ADC values and as such potentially introducing a bias in the study results [Woodhams et al, 2009].
Clinical and imaging data were retrieved from a patient database. The study data were retrieved from a previous imaging study, which received approval from the local institutional ethical committee, and for which all patients provided written informed consent. Thirty-six patients were excluded: 16 did not receive surgery, 5 had predominantly mucinous tumors on the histological evaluation of the surgical specimen and in 15 patients, the histological differentiation grade could not be derived from the pathological reports (including 9 complete responders in whom no residual tumor could be found). The final study population consisted of the remaining 50 patients (37 male, 13 female). Median age was 70 years (range: 49–88). Neoadjuvant treatment consisted either of short-course radiation therapy (RT) (5x5 Gy) or long-course chemoradiation therapy (CRT) (28x1.8 Gy on weekdays with concomitant 2x825 mg/m^2/d capecitabine).

2.2. MR Imaging

The primary staging MRI was performed before the neoadjuvant and surgical therapies. Patients were imaged in a 1.5-T MR magnet (Intera; Philips Medical Systems, Best, The Netherlands), using a phased-array body coil. The standard imaging protocol consisted of standard T2-weighted (T2W) fast spin echo in three orthogonal directions, which were used for clinical staging (TR/TE: 3427/150 msec; Flip angle: 90°; Echo train length: 25; NSA: 6; Acquisition voxel size: 0.78×1.14×5.00 mm; Number of slices: 22; Acquisition time: 5'08"). In addition, axial diffusion-weighted sequence with background body signal suppression (DWIBS, b-values: 0, 500, 1000 s/mm^2; TR/TE: 4829/70 msec; EPI factor: 53, NSA: 4, Acquisition voxel size: 2.50×3.11×5.00 mm; Number of slices: 50 slices; Acquisition time: 10'37") was acquired. Nodal evaluation was performed on an axial 3D T1-weighted gradient-echo sequence (TR/TE: 9.8/4.6 msec; Flip angle: 15°; NSA: 1; Acquisition voxel size: 1.15×1.15×1.00 mm; Number of slices: 200;

Acquisition time: 6'30"), acquired after intravenous administration of gadofosveset trisodium (Ablavar™, Lantheus Medical Imaging, Billerica, MA, USA). All axial sequences were angled in identical planes, perpendicular to the tumor axis as identified on sagittal MRI. The T2W coronal sequence was angled parallel to the tumor axis. Patients did not receive bowel preparation, anti-spasmodic medication or rectal distention before the MR examination.
Apparent Diffusion Coefficient maps in greyscale were automatically generated at the operating system, using a mono-exponential decay model including all three b-values.

2.3. ADC Evaluation

The MR images were analysed by a radiological PhD fellow with 3 years of specific experience in reading rectal MRI examinations who was blinded to the clinical patient data and pathology reports.
Mean ADC was calculated from a sample of three round/oval-shaped ROIs that were manually placed within solid tumour parts (as identified as focal masses showing intermediate signal intensity on the anatomical T2-weighted images) of three independent tumour-containing slices.
The size and position of the ROIs was chosen to include as much of the solid tumor area as possible (Figure III.1).

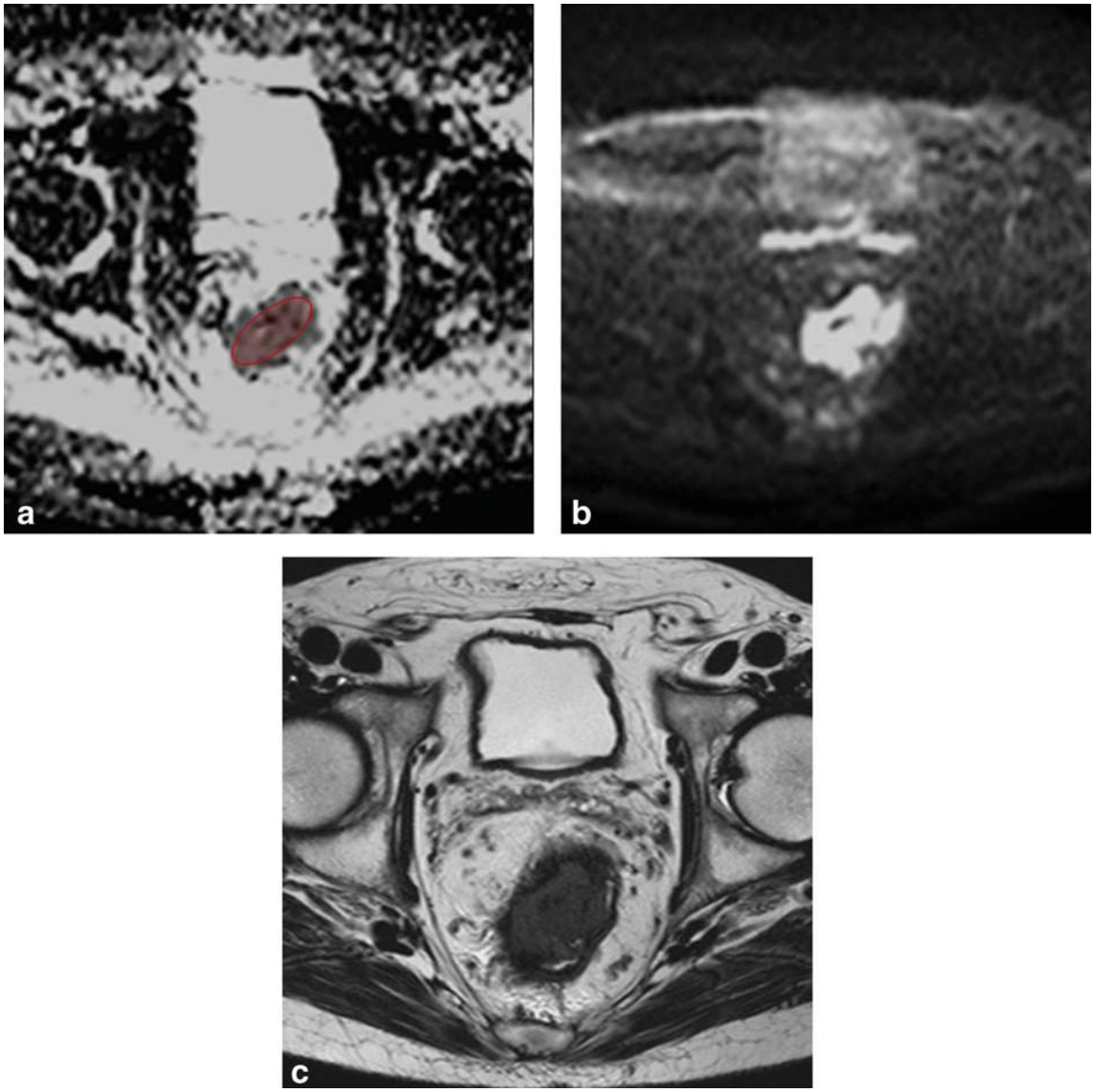


Figure III.1. Example of manual placement of an oval-shaped ROI for measurement of the ADC values for each tumor on the ADC map (a). High b-value (b = 1000 s / mm^2) DWI (b) and T2W (c) images provided respectively functional and anatomical reference.

2.4. Prognostic Factors

Clinical, radiological and histological prognostic factors were derived from the clinical patient database. The clinical factor was the plasmatic CEA level (ng/mL) at the time of diagnosis. The following parameters were retrieved from MRI at primary staging: the mrT stage (mrT1-2, T3, T4), the mrN stage (mrN0, N1, N2) – both reported according to the Sixth American Joint Committee on Cancer TNM staging system – and the MRF status at MRI (free or involved). Histological evaluation of the surgical resection specimen was the reference standard for the histological parameters: tumor differentiation grade and LVI. Differentiation grade of the tumor was scored by the pathologist according to the following grades, used in our institution: 0) poorly differentiated; 1) poorly to moderately differentiated; 2) moderately differentiated; 3) moderately to well differentiated; 4) well differentiated. LVI was reported as absent or present.

For T3 tumors showing extramural growth, the distance in millimeters from the outermost part of the tumor to the MRF was also measured on the primary staging MRI.

2.5. Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 17.0, Inc., Chicago, IL, USA).
Student t-tests (independent-samples t-test) were used to assess differences between means of the following groups: CEA <5 ng/mL vs. ≥5 ng/mL (threshold used in our institution); mrT1-2 (tumor limited to the bowel wall) vs. mrT3-4 (tumor beyond bowel wall); mrN0 vs. mrN1-2 (N+); MRF-free vs. MRF-invaded; and LVI absent vs. LVI present. A one-way analysis of variance (ANOVA) was used to test differences in ADC values between the 5 pre-defined differentiation grade groups, followed by post-hoc Tuckey's test.
Correlation between pre-treatment ADC values and the distance from the outermost part of the tumor to the MRF at primary staging MRI was investigated with determination of the Pearson correlation coefficient.
For all the above mentioned analyses, a p value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Treatment Characteristics

Three patients underwent immediate surgery, whereas the remaining 47 patients underwent surgery after neoadjuvant treatment consisting either of a short-course of radiation therapy (n=28) or a long-course chemoradiation therapy (n=19). Surgery consisted of a low anterior resection (n=39), abdomino-perineal resection (n=9), extended resection (n=1) or Hartmann resection (n=1).
The median time interval between the primary staging MRI and surgery was 59 days (range: 7-281): 52 days for the surgery alone group, 43 days for the patients who received short-course radiation therapy and 135 days for the patients who undergone long-course chemoradiation therapy.

3.2. Clinical and Radiological Findings

At the time of diagnosis, 29 patients had CEA levels lower than 5 ng/mL and 16 patients had CEA levels equal to or above 5 ng/mL. In 5 patients this value was not available at baseline.
Regarding the MRI-based findings, 11 patients had tumors limited to the rectal wall (T1 or T2) while the remaining 39 were considered to be T3 tumors. Seventeen patients were staged as N0, while 33 had positive nodal disease (N1 or N2). The MRF was free in 36 patients and involved by tumor in the remaining 14.

3.3. *Histopathological Findings*

From the analysis of the surgical specimens, 5 patients had poorly differentiated, 9 poorly to moderately differentiated, 31 moderately differentiated, 3 moderately to well differentiated and 2 well differentiated tumors. In 28 patients LVI invasion was absent and in 10 it was present. In the remaining 12 patients this information could not be retrieved from the pathological reports.

3.4. *Correlation between ADC and Prognostic Factors*

The mean tumor ADC for the whole patient population was 1.069±0.162 $\times 10^{-3}$ mm^2/s.
Table III.1 presents the differences in pre-treatment tumor ADC values between the different subgroups.

Prognostic factors	Groups	No. of patients (n=)	Mean ADC (± SD)	*P*
Pretreatment CEA levels*	<5 ng/mL	29	1.073 (±0.158)	0.502[a]
	≥5 ng/mL	16	1.039 (±0.168)	
Pretreatment cT stage	cT1-2	11	1.148 (±0.181)	0.064[a]
	cT3-4	39	1.046 (±0.151)	
Pretreatment cN stage	cN0	17	1.148 (±0.159)	0.011[a]
	cN+	33	1.028 (±0.149)	
Pretreatment MRF status	Free	36	1.099 (±0.169)	0.013[a]
	Invaded	14	0.991 (±0.113)	
Differentiation grade	Poor	5	1.159 (±0.185)	0.025[b]
	Poor-moderate	9	0.981 (±0.117)	
	Moderate	31	1.053 (±0.156)	
	Moderate-good	3	1.177 (±0.118)	
	Good	2	1.316 (±0.016)	
Lymphangiovascular invasion**	LVI absent	28	1.105 (±0.149)	0.159[a]
	LVI present	10	1.029 (±0.121)	

CEA = carcinoembryonic antigen; c = clinical; MRF = mesorectal fascia; LVI = lymphangiovascular invasion; ADC = apparent diffusion coefficient; SD = standard deviation; ADC values given in $mm^2/s \times 10^{-3}$.
[a]Independent-samples t-test.
[b]One-way analysis of variance.
*In five patients, the CEA baseline value was not determined.
**In 12 patients, the LVI could not be retrieved from the pathological reports.

Table III.1. Correlations between pretreatment ADC values and clinical, radiological, and pathological prognostic factors.

Mean ADCs were significantly different for MRF-free vs. MRF-invaded (p=0.013), mrN0 vs. mrN+ (p=0.011), and for the different tumor differentiation grades at histology (p=0.025), with lower ADC values for tumors with involved MRFs, nodal-positive disease and for cancers of less differentiated grades (Figure III.2).

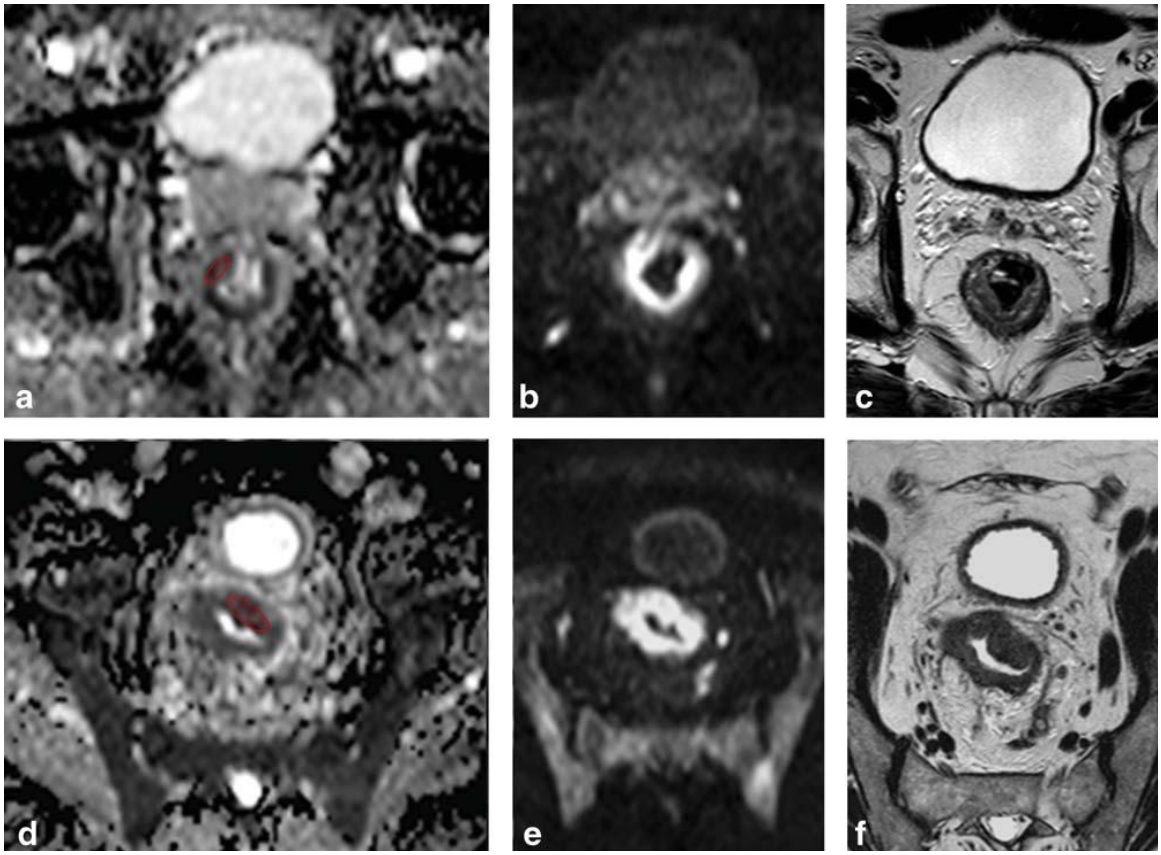


Figure III.2. ADC measurement in tumors of different aggressiveness. In a less aggressive lesion (a, ADC map; b, b = 1000 s /mm^2 image; c, T2W image), which is limited to the bowel wall, without mesorrectal lymph nodes and moderately to well differentiated, the ADC value (1.07 x 10^{-3} mm^2/s) is higher than in a more aggressive neoplasm (d, ADC map; e, b = 1000 s /mm^2 image; f, T2W image), staged as T3N2, with involved MRF and moderately to poorly differentiated (ADC value = 0.94 x 10^{-3} mm^2/s).

The relationship between ADC values and the different histological tumor differentiation grades is given in Figure III.3.

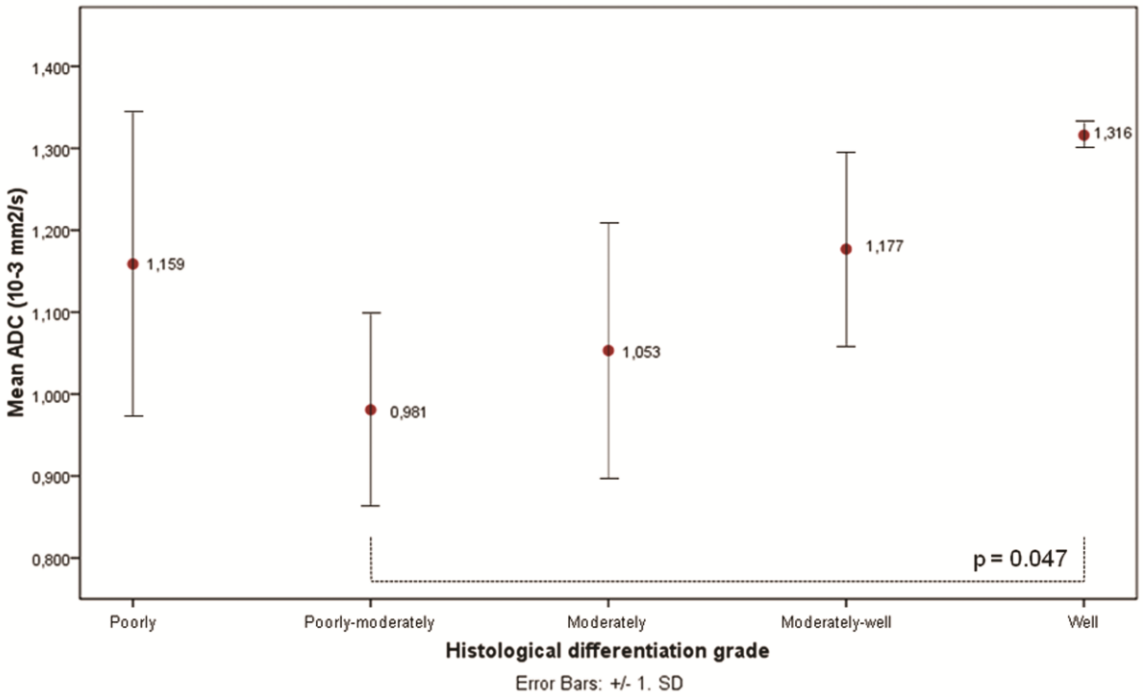


Figure III.3. Comparison of mean ADC values of tumors according to the histological differentiation grade. The whiskers represent the standard deviation. Tuckey's post hoc testing showed that the mean ADCs between poor to moderately differentiated and well differentiated tumors differ significantly (P = 0.047). The relatively high ADC value of the poorly differentiated tumors could partly be related to the small number of patients in this subgroup. Another explanation could be that they have more necrosis at a cellular microscopical level resulting in higher ADC values.

The mean ADC was different between the sub-groups based on the T stage at primary MRI, CEA levels and LVI at histology, with poor prognostic factors (lesions growing beyond the rectal wall, CEA levels ≥ 5 ng/mL, and tumors with LVI) showing lower ADCs, but these differences were not statistically significant.

A significant positive correlation (r=0.374, p=0.019) between ADC values and the distance from the tumor to the MRF was found (Figure III.4).

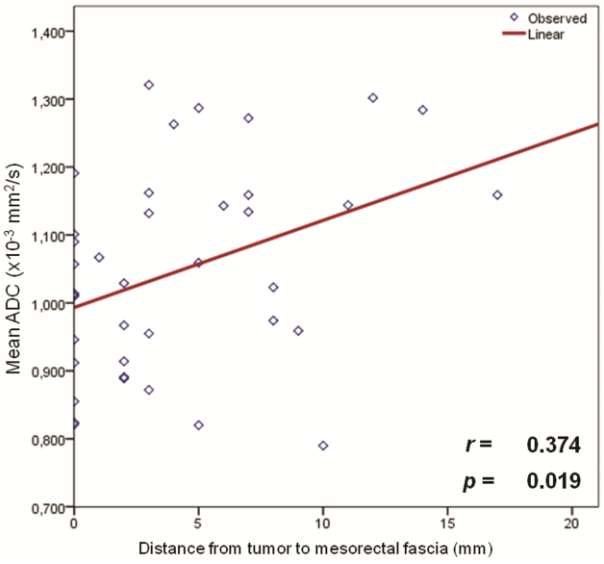


Figure III.4. Correlation between ADC values and pretreatment distance from tumor to MRF.

4. DISCUSSION

The goal of the present work was to assess the value of DW-MRI as a potential non-invasive imaging biomarker of tumor aggressiveness in rectal cancer. The results of our study demonstrate statistically significant correlations between ADC values and the clinical MRF status and nodal status on MR imaging and the tumor differentiation grade at histology. There was no significant correlation between ADC and the T stage at primary MRI, pre-treatment CEA levels, or the presence of LVI at histology.

To the best of our knowledge, a correlation between clinical pre-operative prognostic factors and ADC values in rectal cancer has not been the focus of previous studies. In our study pre-treatment mean ADC was significantly lower for tumors invading MRF or tumors with positive nodal disease. This is an interesting finding as it is proven that both MRF involvement and positive lymph nodes are powerful predictors of a local recurrence and distant metastases. The presence of any correlation between ADC and MRF or nodal status therefore suggests that ADC on itself correlates with prognosis. This could be explained by the fact that ADC values are indirectly derived from a tumor's cellular microarchitecture and may thus reflect the aggressiveness of the tumor tissue profile. This is further supported by the finding that tumors that were less well differentiated showed relatively low ADCs, again suggesting that low ADC values are associated with an unfavorable tumor profile. A recent study showed a similar trend towards low ADC values for poorly-differentiated tumors [Gu et al, 2011].

Although not statistically significant, there was also a trend towards lower ADC values for patients with tumors growing beyond the rectal wall (T3-4) as compared to tumors that were restricted to the bowel wall (T1-2). The lack of significance may partly be due to the relatively small patient population. Another reason could be that the assumption of the subgroups T1-2 and T3-4 having different prognosis (good vs. bad) may not be correct. There is a huge variability in prognosis within the group of T3 tumors: whereas large, bulky T3 tumors are associated with a poorer prognostic outcome and would behave more closely like T4 tumors, the smaller (borderline) T3 tumors are known to have a better prognosis, behaving more closely like T2 tumors. A worsening of prognosis that is associated with a gradual increase of the depth of tumor extension into the surrounding mesorectal fat is described [Wieder et al, 2007]. This is also supported by our findings that showed a significant correlation between ADC and the distance from the tumor to the MRF with lower ADC values associated with a shorter distance between the outermost part of the tumor and the fascia.

Previous studies have investigated the value of pre-treatment tumor ADC as a prognostic factor in terms of prediction of response to chemoradiation in the specific subgroup of patients with locally advanced rectal cancer. Results are conflicting, with some authors demonstrating significantly lower pre-treatment ADC values for the good responders as compared to the non-responders, which suggests that pre-treatment ADC can be beneficial to predict treatment response [Lambrecht et al, 2010; Sun et al, 2010; Dzik-Jurasz et al, 2002]. Others, however, reported that pre-treatment ADC values were not statistically different for responders and non-responders and as such may be limited in predicting treatment outcome [DeVries et al, 2003; Kim et al, 2011; Heo et al, 2010; Kim et al, 2011]. As the extent of response after chemoradiation may also be dependent on the tumor profile, it therefore seems logical to think that initial ADC values may be correlated both with response and the overall prognostic tumor profile as assessed in this current study. The findings of our study and the above mentioned reports may thus be related to each other. However, the assessment of treatment response was

not the focus of our study, and furthermore, the patients undergoing neoadjuvant chemoradiation constituted only a small subgroup (n=19) of the patient population, precluding any meaningful subanalyses.

Our study has some limitations. First, our ADC measurements were obtained by measuring 3 sample ROIs, which may not be fully representative for the overall tumor profile [Roth et al, 2004]. However, this approach was chosen since outlining of the whole tumor volume is very time-consuming and difficult to perform in clinical practice. We aimed to reproduce what happens in the clinical daily work, where time constraints frequently imply that a simpler and quicker way to obtain ADC values will be used. Measurements were obtained by one experienced reader. We acknowledge that this does not allow for evaluation of potential interobserver variations. Second, we chose to correlate ADC with factors derived from the primary clinical staging MRI since we wanted to study the correlation between ADC and the primary tumor profile, i.e. before it was affected by any therapeutic interventions. Hence, we did not use the final pathological T-stage, N-stage and MRF for correlation with ADC, as the majority of patients had undergone chemoradiation therapy prior to surgery, in which setting the T and N stage at histology is no longer representative of the initial tumor profile. After chemoradiation treatment, histopathology is an indicator of treatment response and the prognostic relevance of the definite histological stage seems to be significant mainly in patients with a pathologically complete response [Garcia-Aguilar et al, 2003]. Third, although MRI is known to be a reliable modality for rectal cancer staging, its assessment is observer-dependent and under- or overstaging may have occurred. Nevertheless, for the most relevant prognostic factors for which the association with ADC was significant (MRF and nodal stage), the MRI assessment can be considered accurate to serve as the standard reference: it is known from different validation studies that MRI is highly (>90%) accurate for preoperative assessment of the MRF and reproducible in general hands [Beets-Tan et al, 2001a; Brown et al, 2003a; Ho et al, 2008; Wieder et al, 2007]. Moreover, the nodal stage on MRI was determined by using a lymph node specific contrast agent (gadofosveset trisodium: GDF). This GDF-enhanced MRI approach was shown to be highly accurate with AUCs ranging between 0.94 and 0.98 in a recent publication [Lambregts et al, 2011a]. Finally, it would have been clinically interesting to assess the aggressiveness profile of tumors by means of outcome parameters such as disease-free or overall survival. However, this would require a larger patient cohort and a longer follow-up period which was beyond the scope of our current study.

5. CONCLUSION

In conclusion, ADC values of rectal cancers significantly correlate with prognostic factors including the MRF status, the nodal stage and the histological differentiation grade. There is a tendency towards lower ADC values in tumors with involvement of the MRF, node-positive tumors, poorly differentiated neoplasms, lesions growing beyond the rectal wall, CEA levels higher or equal to than 5 ng/mL, and tumors with LVI, which are the cancers with poorer prognosis. Our study suggests that ADC has the potential to become an imaging biomarker of tumor biological profile.

Chapter IV

Clinical study: Rectal cancer: assessment of complete response to preoperative combined radiation therapy with chemotherapy—conventional MR volumetry versus diffusion-weighted MR imaging

1. INTRODUCTION

The treatment of locally advanced rectal cancer (LARC) has shifted in recent years from a primarily surgical approach with adjuvant radiation therapy toward preoperative combined radiation therapy with chemotherapy (CRT), which results in improved local control and reduced acute and late toxic effects [Sauer et al, 2004]. Moreover, the use of preoperative CRT induces downsizing and downstaging of the primary tumor, yielding a pathologic complete response (CR) (pCR) in up to 24% of patients. A pCR is known to be associated with a favorable oncologic outcome, in regard to both recurrence and survival [Maas et al, 2010]. Habr-Gama et al [2006] reported on 99 patients with a clinical CR who were treated with observation alone ("wait-and-see"): Compared with patients who had residual tumor and were referred to surgery, the 5-year overall and disease-free survival rates were favorable for the observation group. Although still controversial, the trend in treatment is now toward a more conservative policy for patients identified as complete responders after CRT [Bujko et al, 2007; O'Neill et al, 2007]. Traditionally, a pCR is determined with histopathologic examination after surgery. However, if the determination of a CR before surgery would influence the subsequent treatment choice, an accurate clinical assessment of response becomes essential.

Currently used methods, such as digital examination and endoscopy and/or biopsy are good but not infallible. The role of magnetic resonance (MR) imaging in the primary staging of rectal cancer is well established, and it is now part of the standard work-up in many countries. However, its role in restaging after preoperative CRT is not yet clear, partly because to date restaging by using imaging has not influenced the treatment strategy.

MR imaging, like other morphologic imaging techniques (endorectal ultrasonography and computed tomography) is hampered by interpretation difficulties in assessing the presence of residual tumor within areas of radiation-induced fibrosis [Chen et al, 2005; Huh et al, 2008; Barbaro et al, 2010)]. Studies are therefore focusing on the potential added benefit of functional and/or quantitative methods of MR image evaluation. One of these, MR volumetry, was reported to correlate well with downstaging of rectal cancer: A tumor volume reduction rate of around 70%–75% or higher allowed identification of the patients in whom the tumors were downstaged [Barbaro et al, 2009; Dresen et al, 2009)]. Furthermore, a significant association with pCR was reported for patients with a volume reduction rate higher than 75% ([Kang et al, 2010)].

Recently, diffusion-weighted (DW) MR imaging after CRT was shown to be more valuable than morphologic MR imaging for the differentiation between a pCR and residual tumor, because on DW images, viable tumor remnants are more easily recognized, as they appear hyperintense compared with the low signal intensity (SI) of the surrounding nonneoplastic tissue ([Kim et al,

2009; Lambregts et al, 2011c)]. Hence, it can be hypothesized that volumetry of the tumor that is based on SI characteristics on DW images may be more accurate than conventional MR volumetry to distinguish between complete and noncomplete responders. In addition, promising results have been shown for quantitative DW imaging evaluation by measuring the apparent diffusion coefficient (ADC) for the evaluation of treatment response to CRT in patients with rectal cancer [Dzik-Jurasz et al, 2002; Sun et al, 2010; DeVries et al, 2003; Kremser et al, 2003; Hein et al, 2003; Kim et al, 2011; Roth et al, 2004]).
With this study, we aim to determine the diagnostic performance of DW imaging for the assessment of a CR after CRT in patients with LARC by means of volumetric SI measurements and quantitative ADC measurements and to compare the performance of DW imaging with volumetry on standard T2-weighted MR images.

2. MATERIAL AND METHODS

2.1. Patients

Eighty-six consecutive patients diagnosed with LARC at Maastricht University Medical Center (Maastricht, the Netherlands) between June 2006 and May 2010 were considered for inclusion in this retrospective study. Inclusion criteria consisted of *(a)* histopathologically (biopsy-) proved rectal adenocarcinoma; *(b)* locally advanced disease (staged on MR images as cT3–4 and/ or N-category positive); *(c)* neoadjuvant treatment consisting of a long course of preoperative CRT (50.4 Gy radiation plus 2 3 825 mg/m 2 /d capecitabine [Xeloda; Hoffmann-La Roche, Basel, Switzerland]); and *(d)* availability of pre- and post-CRT MR imaging results, including DW imaging results. Exclusion criteria were *(a)* nonresectable and/or metastatic disease and *(b)* insufficient MR image quality (eg, owing to metal implants or movement artifacts). Thirty-six patients were excluded for the following reasons: severe susceptibility artifacts on DW images owing to metal implants (n = 2), neoadjuvant treatment consisting of a short course of 5 Gy radiation on 5 consecutive days plus chemotherapy (n = 3), patient death during neoadjuvant treatment (n = 2), ineligibility to undergo surgery as a result of older age or comorbidity (n = 1), unresectable and/or metastatic disease (n = 9), or pre-CRT MR imaging performed without DW imaging (n = 19). This left a total of 50 patients (median age, 71.5 years; range, 51–90 years) who constituted the final study population. Thirty-six patients were men (median age, 70.5 years; range, 55–90 years) and 14 were women (median age, 76 years; range, 51–82 years). Clinical and imaging data were retrieved from a patient database originating from a previous imaging study approved by the local institutional ethical committee, for which all patients provided written informed consent [Lambregts et al, 2011a].

2.2. MR Imaging

MR imaging was performed at 1.5 T (Intera; Philips Medical Systems, Best, the Netherlands) by using a phased-array body coil. All patients underwent pretreatment MR imaging for primary tumor staging and a second restaging MR imaging examination for response evaluation 6–8 weeks after completion of CRT.

The imaging protocol consisted of the following: *(a)* standard two-dimensional T2-weighted fast spin-echo sequences in three orthogonal directions (sagittal, coronal, axial) (repetition time msec/ echo time msec, 3427/150; flip angle, 90°; echo train length, 25; number of signals acquired, six; acquisition voxel size, 0.78 x 1.14 x 5.00 mm; sections, 22; acquisition time, 5.08 minutes) and *(b)* an axial DW sequence with background body signal suppression [Takahara et al, 2004] and *b* values of 0, 500, 1000 s/mm^2 (4829/70; echo-planar imaging factor, 53; number of signals acquired, four; acquisition voxel size, 2.50 x 3.11 x 5.00 mm; number of sections, 50; and acquisition time, 10.37 minutes). The axial T2-weighted and DW imaging sequences were used for volumetric analyses and were angled in identical planes, perpendicular to the tumor axis as defi ned on sagittal T2-weighted MR images. The coronal T2-weighted sequence was angled parallel to the tumor axis. Patients did not receive bowel preparation, antispasmodic medication, or rectal distention before any of the MR examinations.

2.3. Volumetric Image Evaluation

The MR images were evaluated on a picture archiving and communication system and were independently analyzed by two observers, with 5 (L.C.S.) and 3 (D.M.J.L.) years of specific expertise in reading pelvic MR images. The observers were blinded to each other's results, the clinical patient data, and pathology reports. The readers calculated tumor volumes by manually tracing the tumor boundaries on the axial images and placing free-hand regions-of-interest (ROIs), which provided the sectional area of the lesion for each tumor-containing section (Fig IV.1).

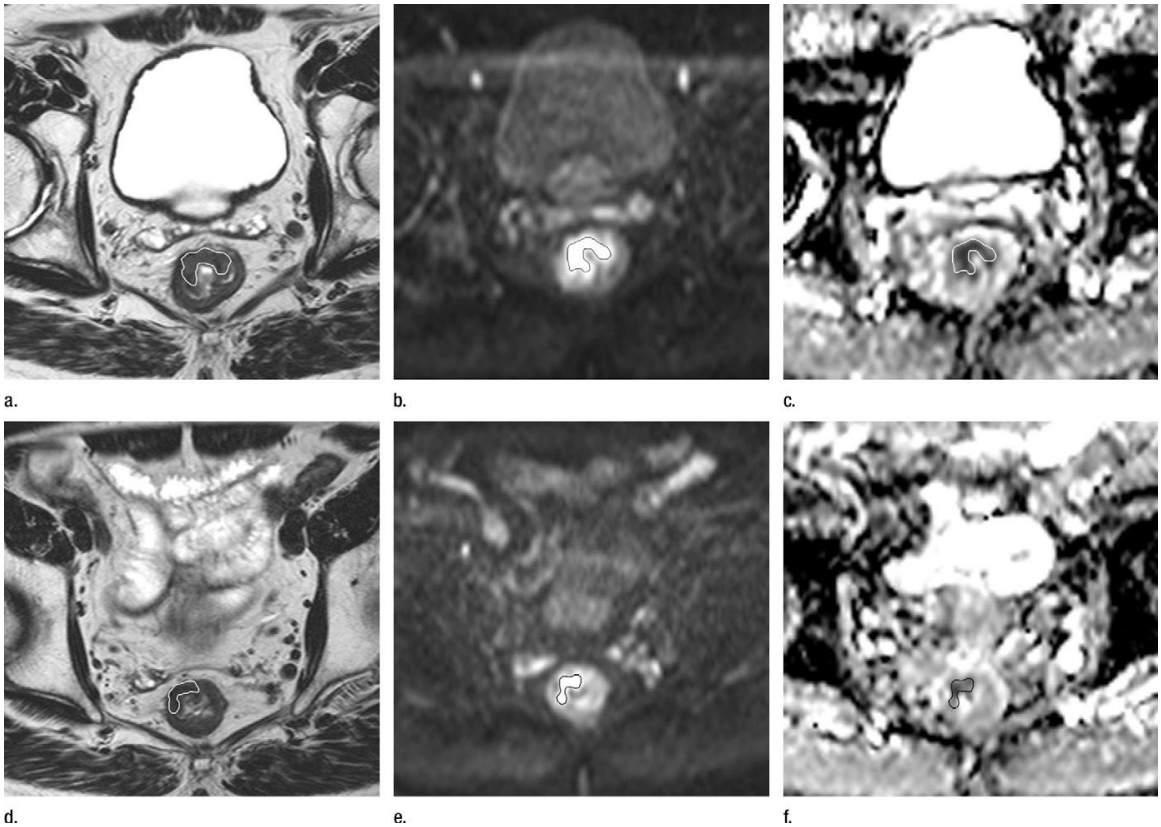


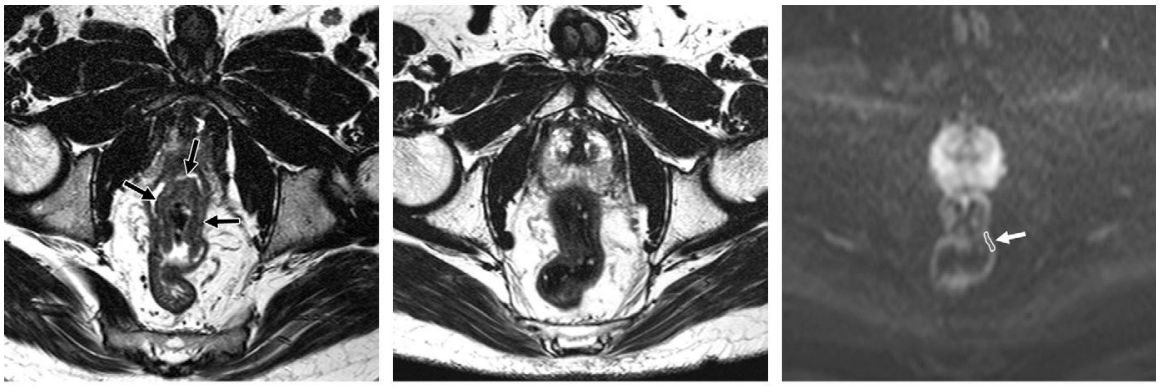
Figure IV.1. Examples of manual tracing of free-hand ROIs for calculation of the sectional area of tumor in each section performed on pre-CRT T2-weighted (a) and DW (b) MR images and on post-CRT T2-weighted (d) and DW (e) MR images. ROIs were

copied from the diffusion images with *b* = 1000 s/mm² to the corresponding pre-CRT (c) and post-CRT (f) ADC maps to calculate mean tumor ADC values. Sectional areas were multiplied by section thickness to determine the tumor volume.

Whole-tumor volume was then calculated by multiplying each cross-sectional area by section thickness. The DW and T2-weighted MR images were analyzed independently and in random order, with a 1-week interval between the two reading sessions. On the T2-weighted images, tumor was defined as areas of isointense signal as compared with the relatively lower hypointense signal of the normal adjacent muscular rectal wall.
On post-CRT T2-weighted MR images, areas of markedly low SI at the location of the primary tumor bed were interpreted as fibrosis. As the risk for residual tumor in these fibrotic areas is known to be ± 50%, they were also included in the volumetric measurements [Vliegen et al, 2008b]. On the DW images, measurements were performed on high– *b* value (1000 s/mm²) images and were based on a visual analysis.
Areas of high SI, compared with the normal bowel wall or background of lower SI tissue, were considered as tumor. For both data sets (T2 weighted and DW), the readers determined *(a)* pre-CRT tumor volume; *(b)* post-CRT tumor volume; and *(c)* the tumor volume reduction ratio (Δ volume), which was calculated as follows: $(TV_{pre} - TV_{post}) \times 100/TV_{pre}$, where TV_{pre} is pre-CRT tumor volume and TV_{post} is post-CRT tumor volume.

2.4. Measurement of the ADC

The diffusion images were exported in Digital Imaging and Communications in Medicine format to an off-line MR workstation, on which ADC maps in gray scale were automatically generated by using a monoexponential decay model including all three *b* values (0, 500, and 1000 s/mm²). ROIs covering the whole tumor volume (as described above) were reproduced on the MR operating system on the diffusion images with *b* = 1000 s/mm² by two independent readers (D.M.J.L. and T.T.), who were blinded to each other's results, the clinical patient data, and pathology reports. The ROIs were then copied from the images with *b* = 1000 sec/mm 2 to the ADC map to calculate mean pre- and post-CRT tumor ADCs (Fig IV.1). When no remaining high SI could be visualized on the post-CRT diffusion images, three sample measurements were obtained of the rectal wall at the former location of the primary tumor (Fig IV.2).



a. b. c.

Figure IV.2. Interpretation of a CR on T2-weighted and DW MR images. (a) Pre-CRT DW image shows that there is a tumor visible in the distal rectum (arrows). (b) Post-CRT T2-weighted MR image shows that a normalized rectal wall is visualized. (c) High- *b* -value (1000 s/mm²) post-CRT DW MR image shows absence of residual tumor, which was based on a lack of hyperintense SI

areas of the bowel wall. To obtain post-CRT ADC measurements, three sample measurements (an example of which is indicated by the arrow) were taken from the normalized rectal wall at the location of the former tumor.

In one patient, ADC measurements were not obtained, because his tumor had an entirely mucinous aspect (completely hyperintense in signal on T2-weighted MR images) without any solid tumor parts. These fully mucinous tumors are known to exhibit high ADC values, which would potentially lead to bias of the study results [Woodhams et al, 2009].

2.5. Standard of Reference

Forty-two (84%) patients underwent total mesorectal excision. The surgical resection specimens were histopathologically examined by dedicated pathologists experienced in colorectal cancer staging. Specimens were examined according to the Sixth American Joint Committee on Cancer TNM staging system. The tumor regression grade (TRG) was evaluated according to the method of Mandard et al [1994]. The response of the primary tumor was graded as follows: pCR (T stage after therapy at histopathologic evaluation, ypT0; TRG 1, no residual tumor cells) or residual tumor (ypT1–4; TRG 2–5, varying from rare residual cancer cells to a solid residual tumor mass).
Eight (16%) patients did not undergo surgery because of strong clinical evidence of a CR (repeated negative findings at sigmoidoscopy and biopsy after CRT). These patients underwent intensive 3-monthly follow-up, with a median local and distant recurrence-free follow-up period of 17 months, which was considered a surrogate end point for a CR.

2.6. Statistical Analysis

Statistical analyses were performed by using software (SPSS, version 16.0; SPSS, Chicago, Ill). Interobserver variability for the three readings (T2-weighted MR volumetry, DW MR volumetry, and ADC), as well as the correlation between the volume measurements on T2-weighted and DW images were analyzed by calculating the intraclass correlation coefficient (ICC) for single measurements (0–0.20, poor correlation; 0.21–0.40, fair correlation; 0.41–0.60, moderate correlation; 0.61–0.80, good correlation; and 0.81–1.00, excellent correlation).
Volumes and ADCs were averaged between the two observers for further analysis. A Student *t* test was used to compare the mean ADCs between the complete responders and noncomplete responders. As the tumor volumes were not normally distributed, a Mann-Whitney *U* test was used to compare the tumor volumes between the complete responder and noncomplete responder groups. A Wilcoxon signed-rank test was used to compare pre- and post-CRT volumes, and a paired-samples *t* test was used to compare the pre- and post-CRT ADC measurements. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic performance in detecting a CR for *(a)* T2-weighted MR volumetry, *(b)* DW MR volumetry, and *(c)* ADC. Corresponding areas under the ROC curve (AUCs), sensitivities, specificities, positive predictive values, and negative predictive values were calculated. For these analyses, cutoff values were determined according to the point nearest to the upper left corner in the ROC curves. Differences in diagnostic performance were analyzed by comparing the ROC

curves according to the method described by DeLong et al [1988]. A difference with a *P* value of less than .05 was considered significant.

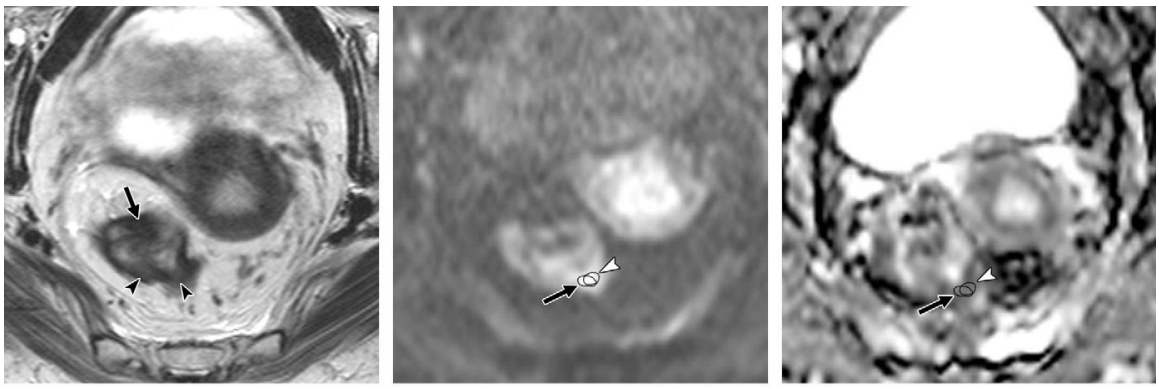
3. RESULTS

3.1. Patient and Treatment Characteristics

Twenty-four patients underwent a low anterior resection, 12 underwent an abdominoperineal resection, and six underwent an extended resection. Histopathologic analysis of the surgical specimen yielded the following fi ndings: Six patients had ypT0, four had ypT1, 13 had ypT2, 18 had ypT3, and one had ypT4 tumor. Six patients had mucinous type adenocarcinoma. The median time between the restaging MR imaging and surgery was 20 days (range, 4–197 days). Together with the eight nonsurgically treated patients, the total number of patients with a CR corresponded to 14 (28%).

3.2. Interobserver Agreement

The interobserver agreement (ICC) for the T2-weighted MR volume measurements was 0.93 on pre-CRT MR images and 0.79 on post-CRT MR images. For the DW MR volume measurements, ICCs were 0.96 on pre-CRT MR images versus 0.75 on post-CRT MR images. For the ADC measurements, ICCs were 0.91 on pre-CRT MR images versus 0.61 on post-CRT MR images. Figure IV.3 illustrates the effect of interobserver variations on the volumetric DW MR and ADC measurements.



a. b. c.

Figure IV.3. Post-CRT images in 79-year-old female patient with a ypT3 residual tumor. (a) T2-weighted MR image shows persistent wall thickening suggestive of residual tumor (intermediate SI = arrowheads) and fibrosis (low SI = arrow). (b) DW MR image shows a small focus of hyperintensity in the bowel wall. To delineate the tumor volume, the ROI was placed as shown by observers 1 (arrow, also on c) and 2 (arrowhead, also on c). The two ROIs resulted in comparable tumor areas (0.48 vs 0.46 cm^2). (c) ADC map derived from the DW images shows that corresponding ADC values were 1.21 versus 1.36 x 10^{-3} mm^2/s for the ROIs placed by the two respective observers. The difference in ADC between the two observers (0.15 x 10^{-3} mm^2/s) for this single measurement was thus larger than the overall difference in mean tumor ADC observed between the complete responder and noncomplete responder groups, which was 0.07 x 10^{-3} mm^2/s for the post-CRT measurements. This example illustrates that small variations in ROI size and/or placement may result in nonnegligible variations in ADC that may substantially influence study results.

3.3. *T2-weighted versus DW MR Volumetry*

The median tumor volumes from T2-weighted MR and DW MR images (mean of two observers) for the whole patient group and for the complete responder versus noncomplete responder groups are displayed in Table IV.1.

Volume and ADC	All (n = 50)	Complete Responders (n = 14)	Noncomplete Responders (n = 36)	P Value*
T2-weighted volume (cm^3)†				
Pre-CRT	21.8 (2.9–538.4)	20.6 (4.2–538.4)	24.3 (2.9–219.0)	.46
Post-CRT	5.5 (0–61.0)	1.2 (0–53.9)	5.6 (0.3–61.0)	.03
Δvolume (%)	−81.4 (20–100)	−92.2 (20–100)	−78.1 (41–92)	<.001
DW volume (cm^3)†				
Pre-CRT	18.0 (1.7–484.9)	11.9 (3.6–484.9)	18.9 (1.7–175.5)	.16
Post-CRT	1.0 (0–17.6)	0.03 (0–1.2)	1.5 (0.2–17.6)	<.001
Δvolume (%)	−95.1 (46–100)	−99.7 (93–100)	−90.2 (46–99)	<.001
ADC ($\times 10^{-3}$ mm^2/sec)‡				
Pre-CRT	1.09 ± 0.18	1.07 ± 0.15	1.10 ± 0.19	.61
Post-CRT	1.43 ± 0.27	1.39 ± 0.24	1.45 ± 0.28	.48
ΔADC (%)	35.6 ± 28.8	35.2 ± 24.7	35.7 ± 30.7	.96

* Volumes were compared for a significance difference by using the Mann-Whitney U test. ADCs were compared by using the Student t test.

† Numbers are medians, and numbers in parentheses are ranges.

‡ Numbers are means ± standard deviations.

Table IV.1. Median volumes and mean ADC values.

Median tumor volumes decreased from 21.8 to 5.5 cm^3 on T2-weighted MR images ($P < 0.001$) and from 18.0 to 1.0 cm^3 on DW MR images ($P < 0.001$). There were no significant differences in pre-CRT volumes between the complete responder and noncomplete responder groups on neither T2-weighted MR images (20.6 vs 24.3 cm^3, $P = 0.46$) nor DW MR images (11.9 vs 18.9 cm^3, $P = 0.16$). The post-CRT volumes were significantly smaller for the complete responder group compared with the noncomplete responder group, both on T2-weighted MR images (1.2 vs 5.6 cm^3, $P = 0.03$) and DW MR images (0.03 vs 1.5 cm^3, $P < 0.001$). The Δ volume was significantly larger for the complete responder group than it was for the noncomplete responder group, both on T2-weighted MR images (- 92.2 vs - 78.1%, $P < 0.001$) and DW MR images (- 99.7 vs - 90.2%, $P < 0.001$). The correlation (ICC) between the volume measurements derived from T2-weighted and DW MR images was 0.97 for the pre-CRT measurements and 0.25 for post-CRT measurements.

3.4. *Tumor ADC Values*

The mean tumor ADC values for the whole patient group and for the complete responder versus noncomplete responder groups are displayed in Table IV.1.

Mean tumor ADC for the two observers increased from 1.09 x 10^{-3} mm^2/sec on pre-CRT MR images to 1.43 x 10^{-3} mm^2/sec on post-CRT MR images ($P < 0.001$). There were no significant differences in pre-CRT, post-CRT, or _ ADC between the complete responder and noncomplete responder groups ($P = 0.61$, 0.48 and 0.96, respectively).

3.5. Diagnostic Performance for Assessment of CR

The ROC curves used to compare the diagnostic performance of the pre-CRT, post-CRT, and Δ measurements of T2-weighted MR volumetry, DW MR volumetry, and ADC for assessment of a CR are shown in Figure IV.4.

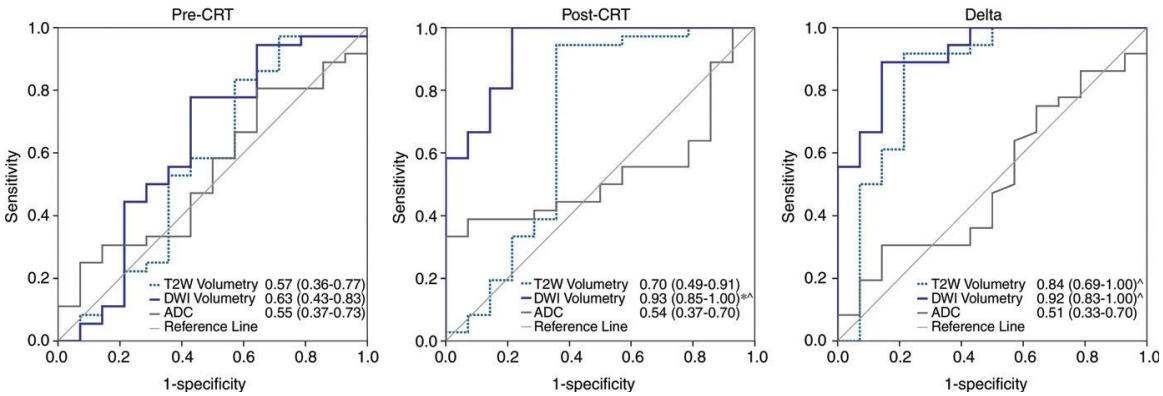


Figure IV.4. Comparison of ROC curves displaying the diagnostic performance for pre-and post-CRT volumes and Δ volume *(Delta)* on T2- and DW MR images and ADC in the assessment of a CR. Numbers = AUC values for each sequence, numbers in parentheses = 95% confidence intervals, * = significant difference in AUC compared with T2-weighted MR volumetry, and ^ = significant difference in AUC compared with ADC.

Corresponding accuracy data are provided in Table IV.2.

Measurement	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy	Optimal Cutoff*
Pre-CRT						
T2 volume	43 (6/14)	83 (30/36)	50 (6/12)	79 (30/38)	72 (36/50)	16.7 cm^3
95% CI	17, 71	67, 93	21, 78	62, 90	57, 83	
DW volume	57 (8/14)	78 (28/36)	50 (8/16)	82 (28/34)	72 (36/50)	12.5 cm^3
95% CI	28, 82	60, 89	24, 75	65, 93	57, 83	
ADC	38 (5/13)	81 (29/36)	42 (5/12)	78 (29/37)	69 (34/49)	0.97 × 10^{-3} mm^2/sec
95% CI	13, 68	63, 91	15, 72	61, 90	54, 81	
Post-CRT						
T2 volume	64 (9/14)	94 (34/36)	82 (9/11)	87 (34/39)	86 (43/50)	1.6 cm^3
95% CI	35, 87	81, 99	48, 97	72, 95	73, 94	
DW volume	79 (11/14)	100 (36/36)	100 (11/11)	92 (36/39)	94 (47/50)	0.15 cm^3
95% CI	49, 95	90, 100	71,100	79, 98	83, 98	
ADC	46 (6/13)	56 (20/36)	27 (6/22)	74 (20/27)	53 (26/49)	1.41 × 10^{-3} mm^2/sec
95% CI	19, 74	38, 72	10, 50	53, 88	38, 67	
Δvolume or ΔADC						
T2 volume	79 (11/14)	92 (33/36)	79 (11/14)	92 (33/36)	88 (44/50)	−88.6%
95% CI	49, 95	77, 98	49, 95	77, 98	75, 95	
DW volume	86 (12/14)	89 (32/36)	75 (12/16)	94 (32/34)	88 (44/50)	−97.5%
95% CI	57, 98	73, 96	47, 92	80, 99	75, 95	
ADC	54 (7/13)	64 (23/36)	35 (7/20)	79 (23/29)	61 (30/49)	25.3%
95% CI	25, 80	46, 79	15, 59	60, 92	46, 74	

Note.—Data are percentages, and numbers in parentheses were used to calculate the percentages. CI = confidence interval, T2 = T2 weighted.

* Cutoff values were chosen according to the point nearest to the upper left corner in the ROC curves.

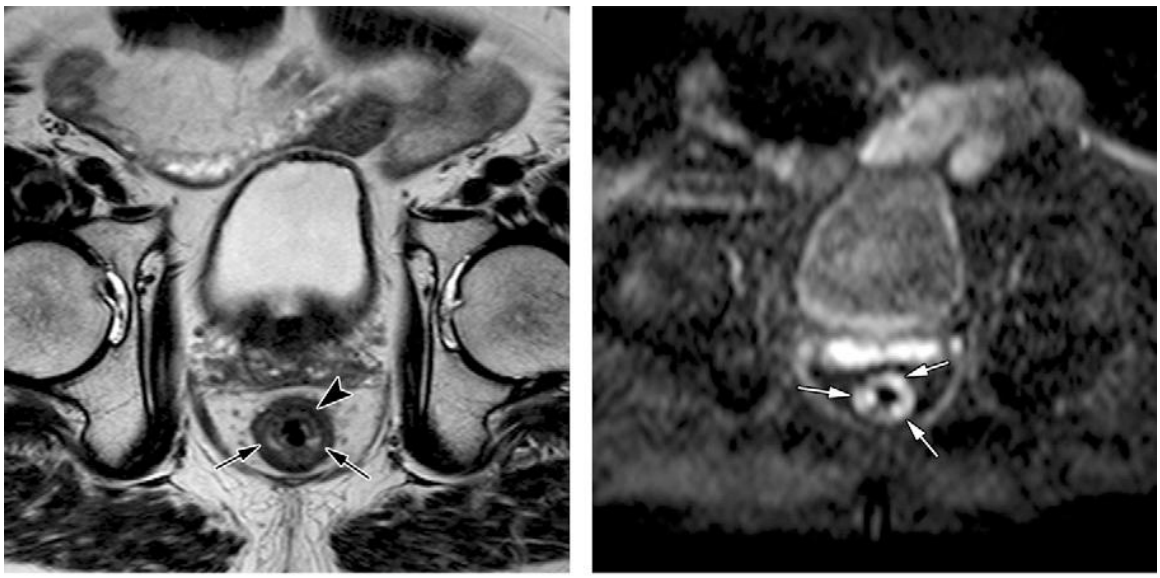
Table IV.2. Diagnostic performance for volume measurements from T2-weighted and DW MR Images and ADC in detection of a CR.

The pre-CRT measurements resulted in AUCs of 0.57, 0.63, and 0.55 for T2-weighted MR volumetry, DW MR volumetry, and ADC, respectively, which were not significantly different from each other (*P* = 0.15–0.85). For the post-CRT measurements, AUCs were 0.70 for T2-weighted MR volumetry, 0.93 for DWMR volumetry, and 0.54 for ADC. The results for DW MR

volumetry were significantly better compared with either T2-weighted MR volumetry or ADC ($P = 0.02$ and $P < 0.001$, respectively). The Δ volumes of T2-weighted MR (AUC, 0.84) and DW MR (AUC, 0.92) were significantly better than Δ ADC (AUC, 0.51; $P = 0.003$ and $P < 0.001$, respectively).
The difference in AUC between the Δ volumes from T2-weighted and DW MR was not significant ($P = 0.42$). The performance of post-CRT DW MR volumetry was equally accurate as the Δ volumes from T2-weighted ($P = 0.31$) and DW ($P = 0.65$) MR.

3.6. Interpretation Errors on DW MR Images

Eleven of the 14 complete responders could be detected on the basis of the absence of high SI on DW MR images. The three false-negative findings on DW MR images were caused by the following reasons: In one patient, high SI caused by a collapsed rectal wall at the location of the primary tumor was erroneously interpreted as residual tumor. In the other two patients, DW MR images showed small areas of high SI at the location of the primary tumor, while histopathologic findings indicated mainly fibrosis, necrosis, and inflammation without any residual tumor cells (Fig. IV.5).



a. b.

Figure IV.5. (a) Post-CRT T2-weighted and (b) DW MR images in 71-year-old male patient with a CR in whom the presence of residual tumor was overestimated by both observers on both images. T2-weighted MR image demonstrates a persistent wall thickening with predominant low SI owing to fibrosis (arrowhead), but also with some areas of intermediate SI interpreted as residual tumor (arrows). On b, hyperintense areas (arrows) were interpreted as residual tumor within the bowel wall. Histopathologic examination revealed no viable neoplastic tissue (ypT0), although some nonneoplastic epithelial tissue of unknown origin was found within the muscular layer, which may explain the difficulties in interpreting the images.

4. DISCUSSION

The goal of our study was to evaluate the diagnostic performance of DW MR imaging for the assessment of a complete tumor response in patients with LARC and to compare it with tumor

volume measurements on conventional T2-weighted MR images. For this purpose, DW MR images were evaluated in twofold: *(a)* by volume measurements of high SI areas on diffusion images with b = 1000 sec/mm^2 and *(b)* by measurement of tumor ADC values. The results of our study demonstrate that post-CRT DW MR volumetry provides high diagnostic performance (AUC, 0.93) for the assessment of a CR and is significantly more accurate than is post-CRT T2-weighted MR volumetry (AUC, 0.70) or post-CRT ADC (AUC, 0.54). The post-CRT DW MR volumetry was equal in performance to volume reduction measurements (Δ volume) of both T2-weighted and DW MR (AUC, 0.84 and 0.92, respectively). Pre-CRT DW MR and T2-weighted MR volumetry, as well as ADC, were not reliable to identify a CR, with AUCs ranging between 0.51 and 0.63.

Previously published data addressed the value of rectal tumor volumetry on standard T2-weighted MR images for the assessment of response after CRT and showed conflicting results. Kang et al [2010] reported a significant association with pCR for patients with a tumor volume reduction rate of more than 75%. Kim et al [2005] could not confirm these findings and showed no difference in the tumor volume reduction rates between patients with pCR and those with residual disease. The findings of our study showed that volume reduction measurements performed either on T2-weighted MR images or diffusion images with b = 1000 sec/mm^2 can be used to assess a CR, with an overall accuracy of 88% for both techniques. Of interest, however, was our finding that tumor volumetry performed on post-CRT DW MR images only was equal in performance to the tumor volume reduction measurements on T2-weighted and DW MR images, suggesting that evaluation of pre-CRT images may not even be necessary. The latter is further supported by the fact that, in our study, pretreatment measurements were not reliable for the assessment of a CR. Another interesting finding was that volumetry on post-CRT DW MR images was significantly more accurate than that on post-CRT T2-weighted MR images for assessing a CR. Apparently, the tumor volumes measured on the basis of the presence (or absence) of high-SI areas on DW MR images better represented the actual presence of residual tumor. On morphologic post-CRT MR images, it is more difficult to measure volumes because it is difficult to define which of the fibrotic areas are still suspicious for tumor and should be included in the volume measurements and which should not. We experienced that those difficulties were less pronounced on DW MR images and that, on DW MR images, the delineation of residual tumor was more clear-cut. This was also reflected in the poor correlation (ICC, 0.25) between the post-CRT tumor volumes measured on T2-weighted and DW MR images.

Given the high diagnostic performance of post-CRT DW MR volumetry on the basis of signal perception on images with b = 1000 sec/mm^2, it could be hypothesized that a visual evaluation of whether or not a high SI suggestive of residual tumor is remaining will be sufficient, and volumetric measurements are not even required. Such a visual approach would also be more practical and far less time consuming. Previous authors [Kim et al, 2009; Lambregts et al, 2011c] have already shown good results for a visual analysis of DW MR images. In these reports, the value of adding DW MR imaging to standard MR imaging was assessed by evaluating the DW and T2-weighted MR images side by side and comparing findings of this evaluation with those on T2-weighted MR images only. Kim et al [2009] reported an AUC of 0.82–0.88 for the combined reading of standard MR images plus DW MR images, results comparable to those of Lambregts et al [2011c] who reported AUCs ranging between 0.78 and 0.80 for three independent readers. In our study, we found an even higher AUC (0.93) for the assessment of a CR with DW MR imaging. A possible explanation could be that, in our study, we evaluated the DW MR images independently from T2-weighted MR images and with objective volume measurements, whereas

in the above-mentioned works, T2-weighted and DW MR images were read side by side and by means of subjective interpretation. For example, if a radiologist has already determined a strong suspicion of residual tumor on the basis of the T2-weighted MR image morphologic findings, he or she will not be eager to alter the diagnosis even if the DW MR image would show the contrary. This factor, together with the knowledge that, in oncology, one should better err on the "safe" side and, in case of doubt, should best diagnose a patient as having residual disease than to potentially incorrectly categorize that patient as having a CR, might have incorporated some bias in the evaluation of DW MR images in published literature.

In our study, this bias was eliminated, since the definition of a pCR on a DW MR image was solely based on the absolute absence of hyperintense areas within the rectal wall and the DW MR images were evaluated independently from the T2-weighted images.

Despite our favorable results for DW MR imaging, we acknowledge that it remains difficult to differentiate between patients with a CR (TRG 1) and patients with small microscopic clusters of residual tumor (TRG 2). Furthermore, it is difficult to obtain a precise correlation between DW MR imaging findings and the underlying histopathologic findings at a microscopic level. Further studies are required to address this issue.

In our study, we failed to demonstrate a benefit for pre-CRT ADC, post-CRT ADC, or Δ ADC measurements to differentiate between patients with a CR and residual tumor. A possible explanation could be that ADC measurements are more subject to measuring errors, because of the inherently low discriminatory power and lesion conspicuity on ADC images. Even subtle variations in ROI size and ROI positioning between two readers may result in substantial variations in ADC.

We believe that this phenomenon significantly contributed to the low performance of ADC in our study to precisely distinguish between complete and noncomplete responders. This factor is less an issue when the response groups are more roughly categorized in "responding" and "nonresponding" patient groups, as was done by a number of previous authors [Hein et al, 2003; Sun et al, 2010; DeVries et al, 2003; Kremser et al, 2003; Dzik-Jurasz et al, 2002]. Obviously, such large subcategories will require less precise discrimination methods and is the reason why we believe that these published data have shown more favorable results for ADC.

There were some limitations to our study design. First, eight of 14 complete responders were classified in a group with a wait-and-see approach and histopathologic findings were only available from the biopsy specimen. It should be stressed, however, that these patients are classified in a group with a very strict follow-up protocol, including regular (3-monthly) clinical, endoscopic (with biopsy), and imaging examinations and that, to this date (at 17 months of follow-up), none have developed recurrent disease. A second issue is that a proportion of the included patients had relatively small tumors, which can be explained by the current trend in our institution to stratify an increasing number of small rectal cancers into the pre-CRT regimen. Finally, we acknowledge that, ideally, our study design should also have included an evaluation of intraobserver variability. This was, however, not practically feasible owing to the highly time-consuming methods required to obtain the volumetric and ADC measurements.

5. CONCLUSION

In conclusion, post-CRT volumetry on DW MR images was significantly more accurate than was post-CRT volumetry on T2-weighted MR images to assess a CR after CRT in patients with LARC.

Post-CRT DW MR was equally as accurate as volume reduction (Δ volume) measurements on either DW or T2-weighted MR images. Pre-CRT volume measurements were not accurate. The above findings suggest that evaluation of post-CRT DW MR images can be sufficient and pre-CRT images do not necessarily have to be evaluated. ADC measurements were not reliable for the assessment of a CR.

Chapter V

Clinical study: Tumour ADC measurements in rectal cancer: effect of ROI methods on ADC values and interobserver variability

1. INTRODUCTION

At present, the standard treatment for patients with locally advanced rectal cancer consists of a long course of neoadjuvant chemoradiation treatment (CRT) followed by surgical resection. As surgery is routinely performed in each patient—regardless of the response to treatment—response evaluation after CRT has so far not been a major issue. Nowadays there is, however, a trend towards minimally invasive treatments instead of standard surgery for well-responding patients [Habr-Gama e tal, 2006; Lezoche et al, 2008; Maas et al, 2010]. Accurate response assessment then becomes relevant, as it may directly influence treatment planning. ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) and MRI have been most extensively studied for response evaluation, but these techniques suffer from limitations in the interpretation of fibrotic scar tissue and inflammation [Barbaro et al, 2010; Capirci et al, 2004]. Diffusion-weighted MR Imaging (DWI) is a functional imaging technique that analyses differences in the extracellular movement of water protons to discriminate between tissues of varying cellularity [Bammer, 2003]. Different publications on DWI have shown its potentially beneficial role for the detection and characterisation of malignant tumours [Koh and Collins, 2007; Bruegel et al, 2008; Lim et al, 2009]. In addition, changes in tumour diffusion during and after treatment are indicative of tissue changes on a cellular level and may be used to evaluate treatment response [Patterson et al, 2008; Padhani et al, 2009]. Previous studies in a variety of tumour types have suggested that quantitative interpretation of the apparent diffusion coefficient (ADC) can be used as a biomarker for response to treatment [Theilmann et al, 2004; Cui et al, 2008; Koh et al, 2007; Jain et al, 2010]. For rectal cancer patients specifically, a benefit for treatment response evaluation by measuring tumour ADC values before [Dzik-Jurasz et al, 2002; Sun et al, 2010; Roth et al, 2004; Lambrecht et al, 2010], during [Dzik-Jurasz et al, 2002; Sun et al, 2010; Roth et al, 2004; Kremser et al, 2003; Hein et al, 2003], and after chemoradiation treatment has been suggested [Kim et al, 2011; Kim et al, 2009]. Nevertheless—as also previously pointed out in a review by Patterson et al [2008]—there is no consensus yet on the true clinical value of ADC measurements for response assessment in rectal cancer. This is because the available literature consists of mainly small-scale studies with conflicting results. Moreover, in most studies, DWI evaluation was only performed by a single reader and ADC measurements by a variety of methods for region of interest (ROI) placement. Whereas some authors included the whole tumour volume [Sun et al, 2010; Roth et al, 2004; Lambrecht et al, 2010; Kim et al, 2011; Seierstad et al, 2007], others included only a single tumour slice [Dzik-Jurasz et al, 2002; Hein et al, 2003] or small tumour samples [Kim et al, 2009], which may contribute to the large variety in reported ADC results. It remains unclear whether ROIs for ADC measurements should ideally incorporate the entire tumour volume or only a representative tumour section. Furthermore, none of the studies focusing on rectal tumour ADC have addressed the issue of interobserver

variability, which is a non-negligible factor when considering the use of ADC as a potential marker for response in clinical practice.
The purpose of the current study is to assess the influence of ROI size and positioning on interobserver variability and ADC values when measuring tumour ADC before and after chemoradiation treatment in patients with locally advanced rectal cancer. We aim to determine which method offers the most reproducible results in order to provide a reference for further studies.

2. MATERIALS AND METHODS

2.1. Patients

This study retrospectively evaluated 46 patients who were treated for locally advanced rectal cancer between 2006 and 2010. Clinical patient data were retrieved from a patient database originating from a previous imaging study approved by the local institutional review board, for which the patients provided written informed consent. Thirty-four patients were male and 12 were female. Median age was 70 years (range 49–88). Inclusion criteria consisted of [a] histologically (biopsy) proven rectal adenocarcinoma, [b] locally advanced disease, defined on primary staging T2-weighted MRI by an experienced gastrointestinal radiologist as tumour in the distal rectum (≤5 mm from the anorectal junction), threatened or involved circumferential resection margins (≤2 mm margin between the tumour and mesorectal fascia) and/or positive nodal stage (≥1 suspicious nodes, i.e. >5 mm in size and/or heterogeneous signal intensity and/or irregular border), [c] treatment consisting of a long course of preoperative CRT (50.4 Gy radiation+ 2 × 825 mg/m^2/day capecitabine) followed by surgical resection and [d] availability of pre- and post-CRT MR imaging including DWI. Patients with non-resectable and/or metastatic disease were excluded. Mucinous tumours are known to have a very low cellular density and will therefore exhibit high ADC values [Woodhams et al, 2009]. As this may bias the study results, patients with predominantly mucinous appearing tumours (identified as predominantly high signal lesions on T2-weighted MRI) were also excluded.

2.2. MR Imaging

Patients did not receive bowel preparation or spasmolytics. Imaging was performed at 1.5T (Intera; Philips Medical Systems, Best, The Netherlands) using a phased array body coil. All patients underwent a pre-treatment MRI for primary tumour staging and a second, restaging MRI for response evaluation 6–8 weeks after completion of CRT. The imaging protocol consisted of standard 2D T2-weighted (T2W) fast spin-echo sequences (FSE) in three orthogonal directions and an axial DWI single-shot echo planar imaging sequence, according to the method of diffusion-weighted imaging with background body signal suppression (DWIBS), acquired with b-values of 0, 500 and 1000 s/mm^2 [Takahara et al, 2004]. The sequence parameters are displayed in Table V.1.

	T2W FSE	DWI*
Repetition time (ms)	3427–8456	4829
Echo time (ms)	130–150	70
Echotrain length	25	1
In plane resolution (mm × mm)	0.78×1.14	2.50×3.11
Section thickness (mm)	3–5	5
Section gap (mm)	2	−1
No. of sections	22–30	50
No. of signals acquired	6	4
Sensitivity encoding (SENSE) factor	-	2
Echo planar imaging (EPI) factor	-	53
Acquisition time (min)	5.08–6.03	10.37

Table V.1. Sequence parameters. * DWIwas acquired with b values of 0, 500 and 1000 s/mm^2

The axial T2W and DWI sequences were angled in identical planes and were planned perpendicular to the tumour axis as defined on sagittal MRI. ADC maps in greyscale were automatically generated at the operating system, using a monoexponential decay model including all three b-values.

2.3. *Image evaluation*

The MR images were independently analysed by two radiological researchers (DMJL and TT), who performed tumour ADC measurements on the pre- and post-chemoradiation images. The readers were blinded to each other's results, the clinical patient data and pathology reports. Mean tumour ADC was evaluated by manually drawing regions of interest (ROI) on the high b-value (b1000) diffusion images and copying them to the corresponding ADC map (Fig. V.1).

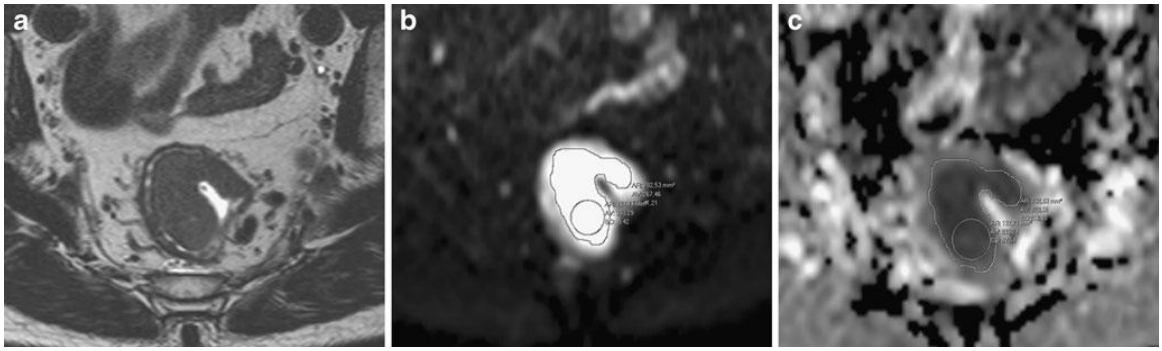


Fig. V.1. Axial T2-weighted image (a), b1000 diffusion image (b) and ADC map (c) of a male patient with a tumour in the rectum. For the whole-volume and single-slice methods, ADC was measured by drawing freehand ROIs along the high signal intensity border of the tumour on the b1000 images (b) to cover the entire tumour area. ROIs were copied to the ADC map (c) to calculate ADC. For the solid sample method, tumour ADC was measured by drawing three oval- or round-shaped ROIs within the most solid tumour areas.

The mean ADC + standard deviation (SD) and the number of pixels per ROI was recorded for each individual measurement. On the pre-treatment b1000 diffusion images, tumour was defined

as a focal mass showing high signal intensity compared with the signal of the normal adjacent rectal wall and corresponding with the tumour (mass showing intermediate signal intensity) on the anatomical T2-weighted MRI. On the post-chemoradiation DWI, tumour was defined as focal areas of residual high signal on the b1000 images within the location of the primary tumour bed and/or corresponding with residual tumour on T2-weighted MRI (Fig. V.2).

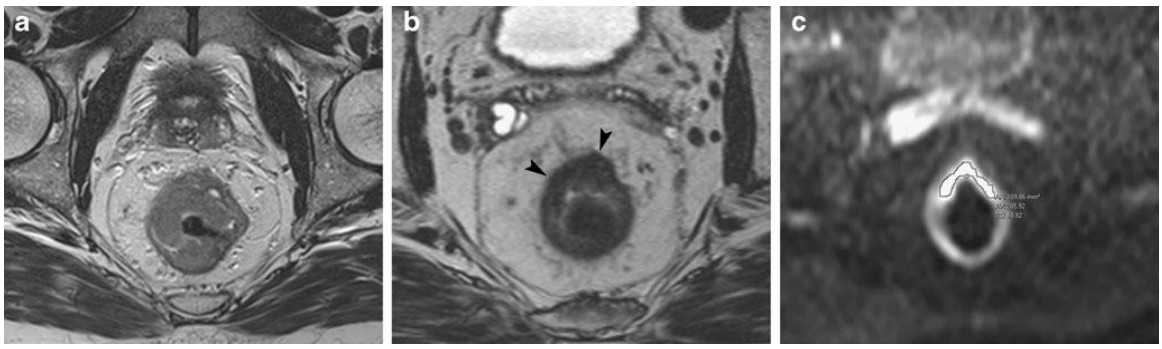


Fig. V.2. Axial pre- (a) and post-treatment (b) T2-weighted images of a male patient with a rectal tumour. After treatment, the tumour has undergone mainly fibrotic changes (arrowheads). On the corresponding b1000 diffusion image, an ROI was drawn along a well-defined area of high signal intensity within the fibrosis, suggestive of residual tumour. At histology, a residual ypT2 tumour was found.

The pre-treatment images were at the readers' disposal when analysing the post-treatment images, in order to compare and identify the location of the tumour. When no remaining high signal could be visualised on DWI, three sample measurements were obtained of the rectal wall at the former location of the primary tumour, of which an example is illustrated in Fig. V.3.

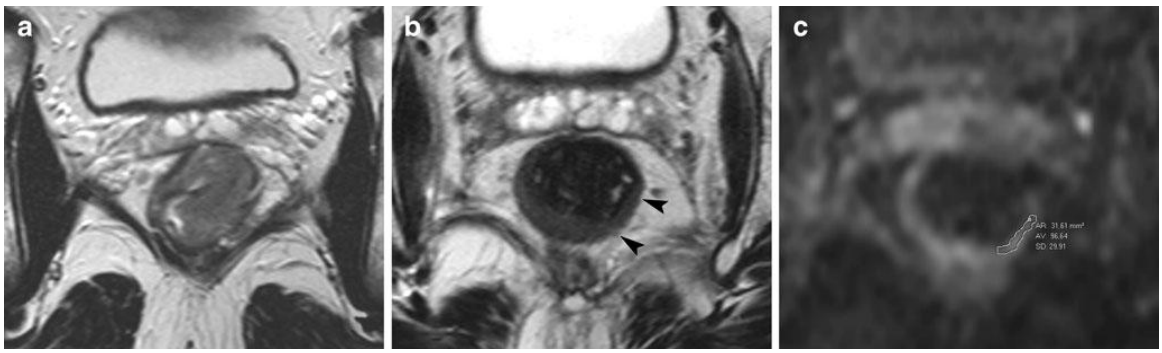


Fig.V.3. Fig. 3 Axial T2-weighted images of a male patient with a rectal tumour before (a) and after (b) chemoradiation treatment. After CRT, the rectal wall has normalised (arrowheads). On the corresponding b1000 diffusion image (c), no high signal was observed and ROIs were placed within the rectal wall at the location of the primary tumour to measure post-treatment ADC. At histology, the patient had undergone a complete response.

2.4. ROI protocols

Mean tumour ADCs were measured according to three distinct ROI protocols: [a] 'Whole-volume', [b] 'Single-slice' and [c] 'Solid tumour samples'. For the whole -volume method, freehand ROIs were drawn along the border of the high signal of the tumour on the b1000 images to cover the entire tumour area of each consecutive tumour-containing slice. Mean ADC (+SD) was obtained for each slice and ADC values were averaged to calculate the mean ADC of

the whole tumour volume. For the single-slice method, a single freehand ROI was drawn in the same way (along the border of the tumour), but only on a single slice containing the largest available tumour area. For the third method, mean ADC was calculated from a sample of three round/oval-shaped ROIs that were placed within the most solid tumour part (as identified on T2W-MRI) of three independent tumour-containing slices, which an example is illustrated in Fig. V.1.

2.5. Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16.0, Inc., Chicago, IL, USA). Interobserver variability for the tumour ADC measurements of the two readers for the pre- and post-CRT ADC measurements and for each individual ROI method was analysed according to the method of Bland and Altman and by calculating the intraclass correlation coefficient (0.00–0.20 poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81–1.00 excellent correlation). ADCs were averaged between the two observers for further analyses. A paired samples *t*-test was used to compare [a] the pre- and post-treatment ADCs and [b] the tumour ADC values obtained by the three different ROI methods. For each patient, the average variance was calculated over the different slice measurements, weighted with the number of pixels. The mean SD for each patient was calculated as the square root of the variance. The variance (mean for the whole patient group) of the different ROI measurement methods and for the pre- and post-CRT measurements was compared using the F-statistics with the total number of slices as the degree of freedom. *P* values <0.05 were considered statistically significant.

3. RESULTS

3.1. Patient and treatment characteristics

Twenty-seven patients underwent a low anterior resection, 15 an abdominoperineal resection and 4 more extended surgery. At histology 6 patients had a ypT0, 5 ypT1, 14 ypT2, 20 ypT3 and 1 a ypT4 status. Thirty-three patients had a ypN0, 9 ypN1 and 4 ypN2 status.

3.2. Effect of ROI methods

The mean tumour ADCs, SDs and total ROI sizes are displayed in Table V.2 for the pre- and post-treatment measurements of each respective ROI protocol.

	Pre-CRT	Post-CRT	*P*
Whole-volume ROIs			
Mean ADC (*10^{-3} mm^2/s)	1.10	1.44	<0.001
SD	0.26	0.25	0.41
Total ROI size (mm^2)	7275	767	<0.001
Single-slice ROIs			
Mean ADC (*10^{-3} mm^2/s)	1.10	1.48	<0.001
SD	0.24	0.23	0.35
Total ROI size (mm^2)	490*	157*	<0.001
Solid sample ROIs			
Mean ADC (*10^{-3} mm^2/s)	1.02*,**	1.41**	<0.001
SD	0.19*,**	0.20*	0.14
Total ROI size (mm^2)	696*,**	220*,**	<0.001

Table V.2. Influence of choice of regions of interest (ROIs). Note.-ADCs and ROI sizes were compared by means of a paired t-test. SDs were compared as variances by means of F-statistics * indicates a significant difference compared with whole-volume ROIs ** indicates a significant difference compared with single-slice ROIs

Mean pre-treatment tumour ADC was significantly lower when measured by means of small sample ROIs, compared with the whole-volume ($P < 0.001$) or single-slice protocol ($P < 0.001$), respectively. For the post-CRT measurements there were no significant differences in tumour ADC between the whole-volume ROIs compared with the single-slice ($P = 0.07$) or small sample ROIs ($P = 0.08$), respectively, but the single-slice ROIs resulted in significantly higher ADCs compared with the small sample ROIs ($P = 0.002$). For the pre-CRT measurements, the variance (SD) of the small sample ROI measurements was significantly smaller than for the whole-volume ROIs ($P < 0.001$) and single-slice ROIs ($P = 0.03$), respectively. For the post-CRT measurements, the variance of the small sample ROIs was also smaller than that of the whole-volume ROIs ($P = 0.003$) and single-slice ROIs, although the latter difference was not statistically significant ($P = 0.06$). There were no significant differences in tumour ADC or variance between the whole-volume and single-slice approaches.

3.3. Interobserver variability

Intraclass correlation coefficients between the two readers are provided in Table V.3 for the three ROI protocols.

	Pre-CRT	Post-CRT
Whole-volume ROIs	0.91	0.66
Single-slice ROIs	0.53	0.42
Solid sample ROIs	0.60	0.65

* 0.00–0.20 poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; 0.81–1.00 excellent correlation

Table V.3. Interobserver variability (measured as the intraclass correlation coefficient*) for the different ROI protocols.

The interobserver reproducibility was excellent (ICC 0.91) for the pre-CRT whole-volume ADC measurements, and good (ICC 0.66) for the post-CRT measurements. For the single-slice and solid sample ROIs, the ICCs ranged from 0.42 to 0.65. Figure V.4 displays the Bland-Altman plots for the whole-volume measurements performed pre- and post-CRT.

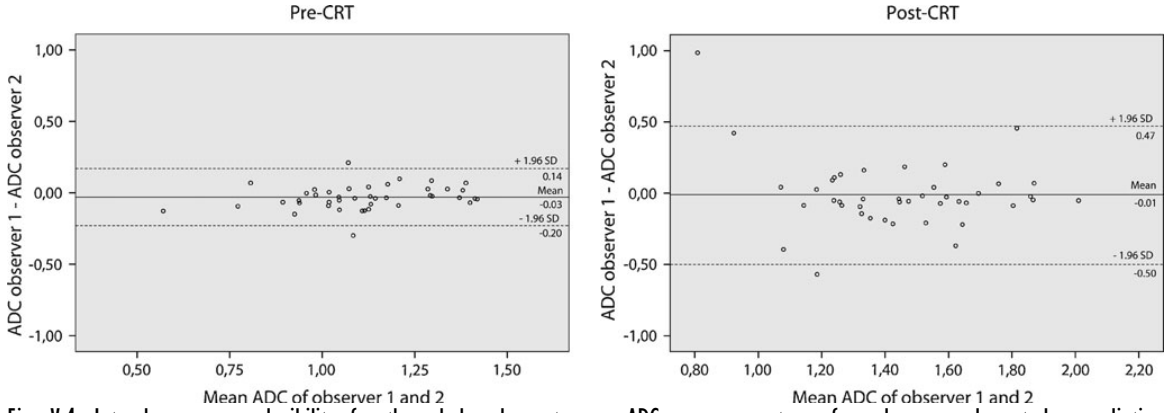


Fig. V.4. Interobserver reproducibility for the whole-volume tumour ADC measurements performed pre- and post-chemoradiation treatment. Bland-Altman plots of the mean ADC of the two observers (x-axis) against the difference in ADC between the two observers (y-axis). The continuous lines represent the mean absolute difference (bias) in ADC between the two observers; the dashed lines represent the 95% confidence intervals of the mean differences (limits of agreement).

4. DISCUSSION

The results of this study show that, when measuring ADC in patients with locally advanced rectal cancer, tumour ADC values and interobserver variability are highly dependent on methods of ROI analysis. ADC measurements obtained from the whole tumour volume are more reproducible than those obtained from single-slice or small sample measurements. In specific pre-treatment whole-volume ADC measurements result in excellent interobserver reproducibility.

The number and size of the ROIs affected the interobserver agreement. When comparing the different ROI protocols, the single-slice and sample ROIs resulted in considerably poorer interobserver agreement (ICC 0.42–0.65) than the whole-volume ROIs (ICC 0.66–0.91), indicating that analysing a larger number of pixels results in more reproducible ADC values.

Interobserver agreement for the whole-volume ADC measurements before treatment was excellent (ICC 0.91), but results after treatment were poorer (ICC 0.66). After chemoradiation, rectal tumours have often undergone massive fibrotic changes and defining a region of tumour residue within the fibrosis may be more difficult (Fig. V.5).

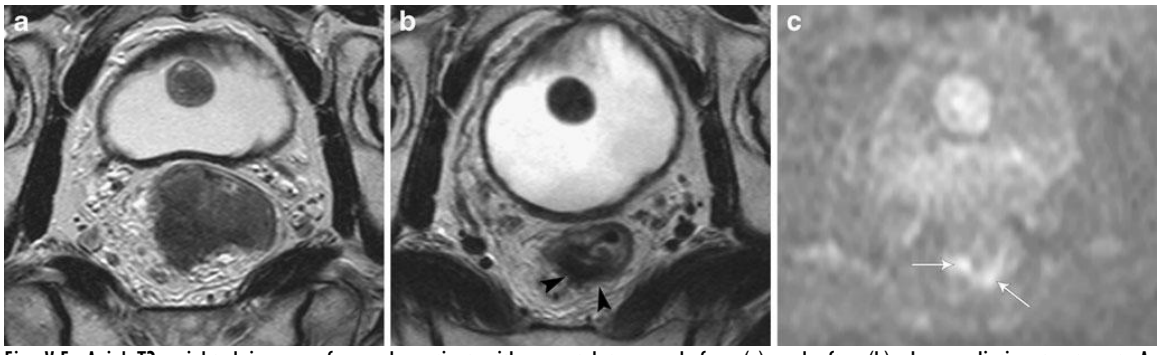


Fig. V.5. Axial T2-weighted images of a male patient with a rectal tumour before (a) and after (b) chemoradiation treatment. An ill-defined residual area of hypointense signal intensity, indicative of fibrosis, is visible after CRT (arrowheads). On the corresponding diffusion image (c) there is still an area of high signal intensity, suggestive of residual tumour (arrows). Because of its irregular aspect and ill-defined borders, however, it is difficult to delineate an ROI, explaining the relatively poor interobserver agreement for the post-CRT ADC measurements. At histology, a ypT1 residual tumour was found.

In cases where the tumour has completely regressed and the bowel wall has normalised or become fibrotically thickened, it can be even more challenging to correctly define an ROI (Fig. 3). After CRT, ADC measurements thus seem to be more affected by the interpretation skills of the reader than before CRT, when the tumour is generally better defined.

The choice of ROIs also significantly influenced the tumour ADC values. On pre-CRT MRI, the whole-volume and single-slice ROIs resulted in significantly higher tumour ADC values than the small sample ROIs. The small sample ROIs only included the most viable solid tumour parts, which may explain the lower ADC values. In this setting, areas of necrosis are likely to be excluded from the ADC measurements, while the presence of necrosis before onset of treatment is in fact believed to be an important indicator when aiming at evaluating response. A previous study of Roth and co-authors showed that whole-volume tumour ADC measurements were a better predictor of response than ROIs chosen only from viable regions of the tumour [Roth et al, 2004]. Although the focus in their study was on perfusion CT in patients with colorectal cancer Goh et al [2008a] also found that, when obtaining pharmacokinetic parameters by applying different ROI sizes and positions, whole tumour volume measurements were the most reliable. The above-described phenomenon may also explain why the whole-volume ADC measurements resulted in a larger variance and higher standard deviations, which is likely to reflect the heterogeneous nature of the tumour, including solid foci, as well as areas of necrosis and fibrosis. Altogether these findings suggest that whole-volume measurements might be a better indicator of tumour viability and may therefore be more suitable for assessment of response. Furthermore, as was also stressed by Goh et al [2008a], if variations in ROI substantially influence the measurements, efforts should be made to standardize their application for clinical use. Interestingly, we observed no significant differences in tumour ADC or SD between the whole-volume measurements and the single-slice approach, suggesting that the latter may also be used as a less time-consuming alternative. However, one should keep in mind that the single-slice method was subject to a much larger interobserver variability and whole-volume measurements thus remain the single most reliable method.

Our study is limited because of its retrospective nature and the relatively small patient numbers. Furthermore, it was sometimes difficult to position regions of interests due to susceptibility artefacts occurring around air-tissue interfaces. This was especially challenging after chemoradiation, in cases where only a limited or no residual tumour could be identified on DWI. Susceptibility artefacts might be minimised by applying rectal wall distension with intraluminal filling, which we have not done in the current study. The specific focus of this study was to determine the effect of ROI size and positioning on tumor ADC evaluation and not to assess the relation between ADC and response, as various previous authors have done [Dzik-Jurasz et al, 2002; Sun et al, 2010; Roth et al, 2004; Lambrecht et al, 2010; Kremser et al, 2003; Hein et al, 2003; Kim et al, 2011; Kim et al, 2009; Seierstad et al, 2007]. As such, we chose not to include a correlation between ADC and histopathological parameters of response.

5. CONCLUSION

In conclusion, variations in ROI size and positioning have a significant effect on tumour ADC values and interobserver variability. The most reproducible results are obtained when measuring ADC of the whole tumour volume. Interobserver variability is larger after chemoradiation treatment than before. These issues should be taken into account when considering the use of ADC as a potential biomarker for response in clinical practice.

Chapter VI

Clinical study: Usefulness of perfusion CT to assess response to neoadjuvant combined chemoradiotherapy in patients with locally advanced rectal cancer

1. INTRODUCTION

The multidisciplinary management of rectal cancer patients has been witnessing a progressive change in the therapeutic approach of locally advanced tumors towards preoperative chemoradiation therapy (CRT), which is useful for tumor downsizing and downstaging, facilitating curative resection, decreasing the local recurrence rate and improving patient survival [Pahlman et al, 1995; Kaminsky-Forrett et al, 1998; Mohiuddin et al, 2000; Medich et al, 2001; Janjan et al, 2001; Valentini et al, 2002; Theodoropoulos et al, 2002]. Tumor downstaging may lead to a partial or complete tumor regression, but in many cases, even if the tumor cell density is significantly decreased the pathologic stage remains the same. The histological tumor response to the preoperative treatment can be assessed by the tumor regression grade (TRG), which may be determined according to different grading systems. One of them, proposed by Dworak et al, was specifically designed for application in rectal cancer [Dworak et al, 1997].

Predicting which tumors will respond well to this therapeutic approach remains a challenge since morphological imaging criteria are unreliable in this regard [Chen et al, 2005; Huh et al, 2008; Barbaro et al, 2010]. As it is becoming increasingly important that preoperative imaging may non-invasively select high-risk patients who could truly benefit from more aggressive multimodality treatment approaches in the preoperative setting [Barrett, 1998; Colorectal Cancer Collaborative Group, 2001], there is a growing interest on functional imaging techniques that can help monitor treatment effects. Both magnetic resonance imaging (MRI) and computed tomography (CT) have shown potential to act as functional biomarkers [Brasch et al, 2000, Harvey et al, 1999, Miles et al, 2000; Dugdale et al, 1999]. Perfusion CT is able to assess vascular physiology within tumors retrieving information about tumor blood flow (BF), blood volume (BV), mean transit time (MTT), and vascular permeability–surface area product (PS) [Goh et al, 2008b, Kambadakone et al, 2009; Kan et al, 2005]. These parameters reflect vascular changes occurring in neoplastic tissue, ultimately related to the angiogenic process: BF reflects vascular supply to the lesion, BV reflects functional vascular volume, MTT reflects the time of blood through the tumor bed under the influence of vascular density, morphology and shunting, as well as interstitial pressure, and PS reflects leakiness of the microvasculature [Bellomi et al, 2007, Goh et al, 2009a].

Two landmark articles have evaluated perfusion CT in the context of rectal cancer assessment prior to CRT, with good response defined as tumor downstaging [Bellomi et al, 2007; Sahani et al, 2005], but to our knowledge there are no published data about its use as a biomarker for treatment monitoring using TRG as endpoint of response to CRT. Thus the purpose of this study was to prospectively evaluate perfusion CT to assess tumor vascularity changes in locally advanced rectal cancer after neoadjuvant CRT and to analyze the correlation between baseline perfusion parameters and tumor response to CRT, as defined by the TRG.

2. MATERIALS AND METHODS

2.1. Patients

Between November 2007 and September 2010, 26 consecutive patients met the inclusion criteria of this prospective study, consisting of: 1) histologically (biopsy) proven non-mucinous rectal carcinoma; 2) locally advanced disease (staged by MRI as T3–4 and/or N positive); and 3) neoadjuvant treatment consisting of long-course CRT followed by surgical resection of the tumor. Patients with a history of allergy to iodinated contrast agents were excluded, as were patients locally non-resectable tumors and/or metastatic disease. These tumors were excluded based on: 1) the assumption that it would be impossible to foresee their downstaging and downsizing after CRT, thus precluding surgery within the time frame defined in the study design, therefore introducing heterogeneity in the study population and 2) the fact that metastatic tumors would not receive the same combined CRT prior to an eventual surgical excision. The study received approval from the local institutional ethical review board, and after the procedure had been fully explained, all patients provided written informed consent. Six patients were excluded: 2 died before surgery, in 3 the CRT protocol was interrupted due to complications and one developed metastatic disease during CRT, forcing a change in the therapeutic regimen. The final study population consisted of 20 patients (12 male, 8 female; median age: 57 years, range: 42–78), staged at baseline MRI as follows: T3N0 (n=1), T3N1 (n=13), T3N2 (n=5) and T4N1 (n=1).

2.2. Treatment

All patients were submitted to 3D-conformal radiotherapy with a total dose of 5040 cGy, delivered in 180 cGy fractions, 5 fractions a week, over a period of 5.5 weeks. Chemotherapeutic agents used concomitantly during the radiotherapy were oral capecitabine (1650 mg/m^2/day, in 2 divided doses) or oral tegafur-uracil (UFT) + calcium follinate (300 mg/m^2/day + 90 mg/day, in 3 divided doses on weekdays). Surgery was performed 6-8 weeks after completion of CRT in all patients.

2.3. CT Technique

All patients underwent baseline perfusion CT the week before the beginning of therapy. Of these, 11 were submitted to a second perfusion CT study, within 2 weeks before surgery (median days after baseline examination: 81; range: 74-96). Regarding the remaining nine patients, one was unavailable for follow-up, two were excluded owing to technical problems (related to peristalsis in the rectum, introducing motion artifacts that may have interfered with the perfusion measurements), and six refused the second examination. Immediately before imaging, patients received intravenous spasmolytic medication (1mL of hyoscine butylbromide). Patients did not receive oral contrast, bowel preparation or rectal distention before the CT examinations. They were imaged in the supine position, in a 64-section multi-detector CT scanner (Lightspeed 64, GE Healthcare Technologies, Waukesha, Wis, USA). A preliminary non-

enhanced scan of the pelvic region (2.5-mm section thickness) was performed to localize the tumor. Then, a board-certified radiologist (with 8 years of experience in GI imaging) selected a 40-mm scanning range for dynamic CT, chosen to include the maximum area of visible tumor. Dynamic study of the imaging volume, with an acquisition in cine mode, was performed as follows: 8 contiguous 2.5-mm reconstructed sections obtained at the same table position, 1-second gantry rotation time, 120 kVp, 300 mA. Scanning was started 5 seconds after i.v. injection of 100 mL of non-ionic iodinated contrast agent (370 mg of iodine/mL), followed by 40 mL of saline solution, via a pump injector at a fixed rate of 4-5 mL/s through a 18–20-G catheter in the ante-cubital vein. A set of 8 images per second during 60 seconds was obtained, corresponding to a total of 480 images.

2.4. Image and data analysis

The image datasets were transferred to an image-processing workstation (Advantage Windows 4.3; GE Healthcare Technologies, Waukesha, Wis, USA). Commercially available software (CT Perfusion 3.0; GE Healthcare Technologies, Waukesha, Wis, USA) was used to calculate perfusion parameters. This software uses a deconvolution algorithm and is based on a mathematical model [Johnson et al, 1966] that describes the distribution of iodinated contrast material in tissue. Assumptions made within the model [Sahani et al, 2005; Lee et al, 2003] include the following: a) the extracapillary interstitial space is a well-mixed and uniform compartment, and b) by considering the interstitial space as a well-stirred compartment, the concentration of solute within this space is a function of time. An adiabatic approximation of the mathematical model [StLawrence et al, 1998] is used in the perfusion software to yield perfusion parameters for a tissue region of interest (ROI). These parameters result from time–contrast enhancement curves of the tissue ROI and the tissue ROI's arterial input. Thus, the resultant perfusion parameters represent mean values for the tissue ROI over the time period of the time–contrast enhancement curves.

CT perfusion analysis was independently performed by a board-certified radiologist (with 4 years of experience in perfusion CT studies) and a senior resident (with no previous experience in perfusion CT), both blinded to each other's measurements, the pathology results and the patient's clinical response to treatment. The arterial input was obtained by drawing a circular ROI (maximum of 10 pixels) placed in the external iliac artery. An arterial enhancement-time curve was automatically generated, as well as functional parametric maps, representing in a color scale pixel values of the following perfusion parameters: BF (in milliliters per 100 g of wet tissue per minute), BV (in milliliters per 100 g of wet tissue), MTT (in seconds) and PS (in milliliters per 100 g of wet tissue per minute). In order to quantify the baseline perfusion parameters of a neoplasm, a free-hand ROI encompassing as much of the tumor area as possible (pre-CRT area range: 292- 1355 mm^2; post-CRT area range: 193-1099 mm^2) was drawn along the visible margins of the lesion at a single table position (where the solid tumor area was largest) and then automatically copied to each functional map (Fig. VI.1).

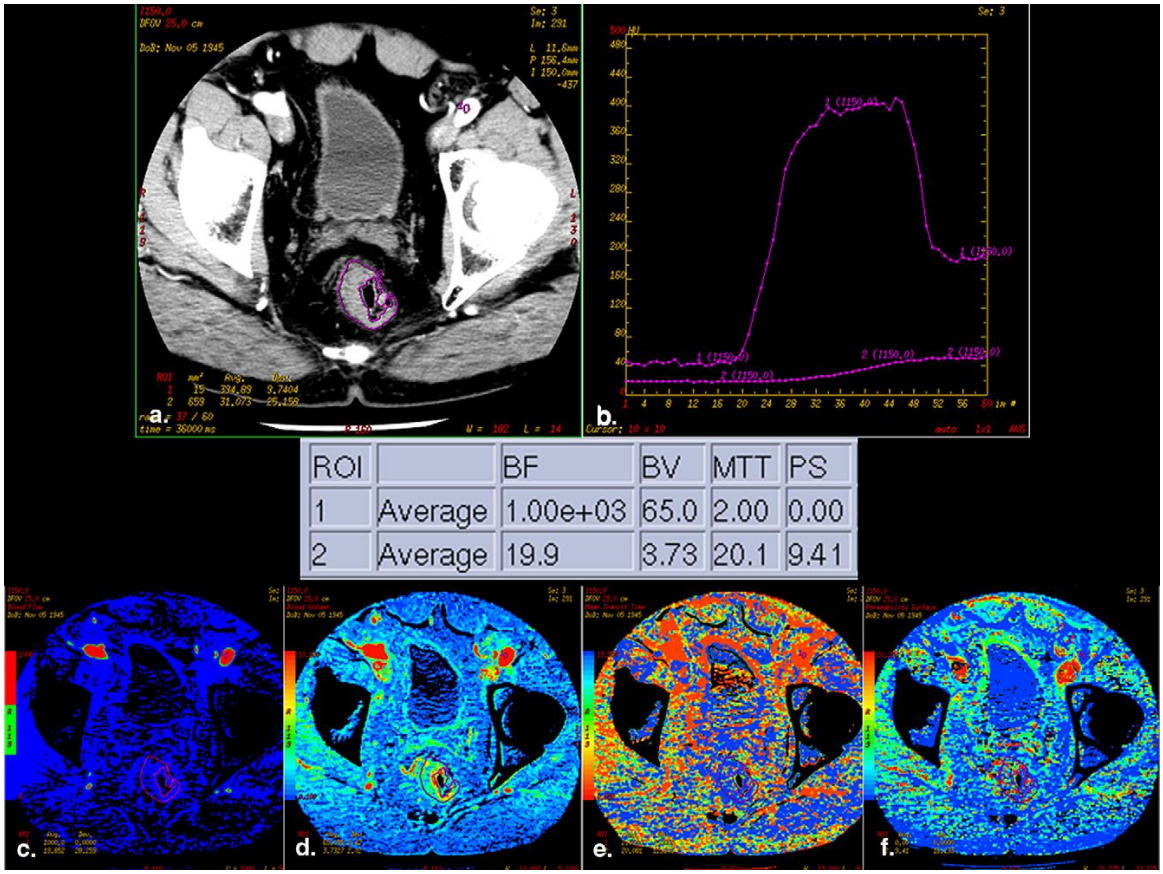


Figure VI.1. (a) Hand-drawn regions of interest (ROIs) along the visible margins of the tumor on axial images. (b) A time-enhancement curve corresponding to the tumor ROI is also generated. Perfusion parameters are computed and values can be presented in a table or in each one of the functional parametric maps: (c) blood flow (BF); (d) blood volume (BV); (e) mean transit time (MTT); (f) permeability-surface area product (PS).

For patients without visible tumor burden after CRT, a ROI was placed over the rectal wall, in the former location of the neoplasm. This methodology was chosen because it was demonstrated that even if no residual tumor burden is visible macroscopically, viable tumor cells persist in the tumor bed in 50% of the cases [Vliegen et al, 2008b]. The variation rate of each perfusion parameter after CRT was calculated as follows: ([Pre-CRT value] – [Post-CRT value]) x 100/(Pre-CRT value).

2.5. Standard of reference

For the histological examination of the surgical specimen, its circumferential resection plane was inked, and it was opened anteriorly and fixed in formalin for 24 h. The whole specimen was then sectioned transversely, every 0.3 cm. The extent of lateral spread in the mesorectum was assessed on each slice, and the shortest distance between the tumor or lymph node and the circumferential resection plane was measured. Specimens were assessed by a semi-quantitative determination of the TRG as proposed by Dworak et al [1997] as the standard of reference. According to the proposed grading system, the tumor response to CRT was defined as follows: grade 0: no regression; grade 1: dominant tumor mass with obvious fibrosis and/or vasculopathy; grade 2: dominantly fibrotic changes with few tumor cells or groups (easy to find); grade 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous

substance; grade 4: no tumor cells, only fibrotic mass (total regression or response). Tumor response after CRT was based on the presence of gross residual tumor: tumors with TRG 0-2 scoring were non-responders, while neoplasms with TRG 3-4 scores were considered responders.

2.6. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 17.0, Inc., Chicago, IL, USA). Interobserver variability between measurements of the two readers for pre- and post-CRT perfusion parameters was analysed by calculating the intraclass correlation coefficient (ICC) (0–0.20, poor correlation; 0.21–0.40, fair correlation; 0.41–0.60, moderate correlation; 0.61–0.80, good correlation; and 0.81–1.00, excellent correlation). Values of perfusion parameters were averaged between the two observers for further analysis. Since most data were not normally distributed, nonparametric tests were used. The median BF, BV, MTT and PS on pre- and post-CRT examinations were compared by means of the Wilcoxon signed ranks test to investigate changes in the perfusion parameters after CRT. The Mann-Whitney U test was used to compare the variation rates in the perfusion parameters after CRT in responders and non-responders and also to compare baseline ROI areas and median BF, BV, MTT and PS of responders and non-responders. For all the above mentioned analyses, a two-tailed p value of less than 0.05 was considered statistically significant. Receiver operator characteristics (ROC) curves were generated to evaluate the diagnostic performance for baseline perfusion parameters in detecting a favorable response (TRG 3-4). Corresponding areas under the ROC curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated. For these analyses, cut-off values were determined according to the point nearest to the upper left corner in the ROC curves.

3. RESULTS

3.1. Treatment characteristics

According to the above mentioned protocols, 10 patients were treated with capecitabine, while UFT was given to the remaining 10. Surgery consisted of low anterior resection (n=15), abdomino-perineal resection (n=4), or extended resection (n=1). The median interval between the baseline perfusion scan and surgery was 101 days (range: 73-112).

3.2. Histopathological findings

After histological analysis of the surgical specimens and application of the Dworak scoring system there were 15 non-responders (2 patients with TRG 0, 4 patients with TRG 1, 9 patients with TRG 2) and 5 responders (3 patients with TRG 3 and 2 patients with TRG 4). Regarding pathological staging, the results showed 2 patients with a ypT0N0, 1 a ypT1N0, 10 a ypT2N0, 4 a ypT3N0, 1 a ypT3N1, 1 a ypT3N2 and 1 a ypT4N1 tumor.

3.3. *Interobserver variability*

The correlation between pre-CRT measurements of both readers was excellent, with ICCs of 0.86 (0.67-0.94), 0.83 (0.62-0.93), 0.92 (0.80-0.97) and 0.95 (0.87-0.98), respectively for the BF, BV, MTT and PS. As for post-CRT measurements, the correlation was good to excellent, with ICCs of 0.77 (0.32-0.94), 0.74 (0.51-0.88), 0.89 (0.63-0.97) and 0.75 (0.52-0.84), respectively for the same perfusion parameters mentioned above. Median differences between readers were the following: for BF, difference on pre-CRT images was 3.75 mL/100g/min and on post-CRT CT was 1,45 mL/100g/min; for pre-CRT BV was 0.10 mL/100g and on post-CRT CT was 0.33 mL/100g; for MTT on pre-CRT scans was 0.55 s and on post-CRT images was 1.70 s; for pre-CRT PS was 0.95 mL/100g/min and for post-CRT examinations was 1.01 mL/100g/min.

3.4. *ROI Areas*

The median baseline ROI area was not significantly different between tumors which responded well (495 mm^2, range: 344-723 mm^2) and poorly-responding lesions (625 mm^2, range: 292-1355 mm^2) (*P*=0.257).

3.5. *Perfusion parameters for assessment of response*

Differences between medians of baseline perfusion parameters across all levels of TRG and in responders and non-responders are summarized in Table VI.1.

	TRG	BF (mL/100 g/minute)	BV (mL/100 g)	MTT (s)	PS (mL/100 g/minute)
Nonresponders (n = 15)	0	94.50 (50.00–139.00)	5.63 (4.65–6.60)	8.09 (4.28–11.90)	6.59 (6.57–6.61)
	1	82.95 (68.00–109.00)	4.85 (4.21–5.92)	5.11 (4.88–5.62)	12.10 (10.70–18.00)
	2	63.70 (41.10–118.00)	5.05 (3.05–9.14)	8.33 (5.72–11.50)	12.50 (6.36–41.40)
	Total	68.00 (41.10–139.00)	5.00 (3.05–9.14)	6.82 (4.28–11.90)	11.40 (6.36–41.40)
Responders (n = 5)	3	38.60 (25.00–58.00)	4.65 (3.58–4.76)	11.10 (10.20–22.50)	13.70 (4.70–20.30)
	4	40.55 (20.10–61.00)	4.73 (4.28–5.17)	15.65 (11.40–20.90)	14.80 (11.90–17.70)
	Total	38.60 (20.10–61.00)	4.65 (3.58–5.17)	11.10 (10.20–22.50)	13.70 (4.70–20.30)
P value (nonresponders vs. responders)		0.013	0.256	0.006	0.407

BF, blood flow; BV, blood volume; MTT, mean transit time; PS, permeability-surface area product; TRG, tumor regression grade.
Minimum and maximum values are provided between parentheses.

Table VI.1. Baseline perfusion parameters across all levels of TRG and in responders and nonresponders to combined chemoradiation therapy.

BF was significantly lower and MTT was significantly higher in responders than in non-responders. No significant difference was found for BV and PS of responders and non-responders. The AUCs for the perfusion parameters were the following: 0.88 for BF, 0.67 for BV, 0.92 for MTT and 0.63 for PS (Figure VI.2).

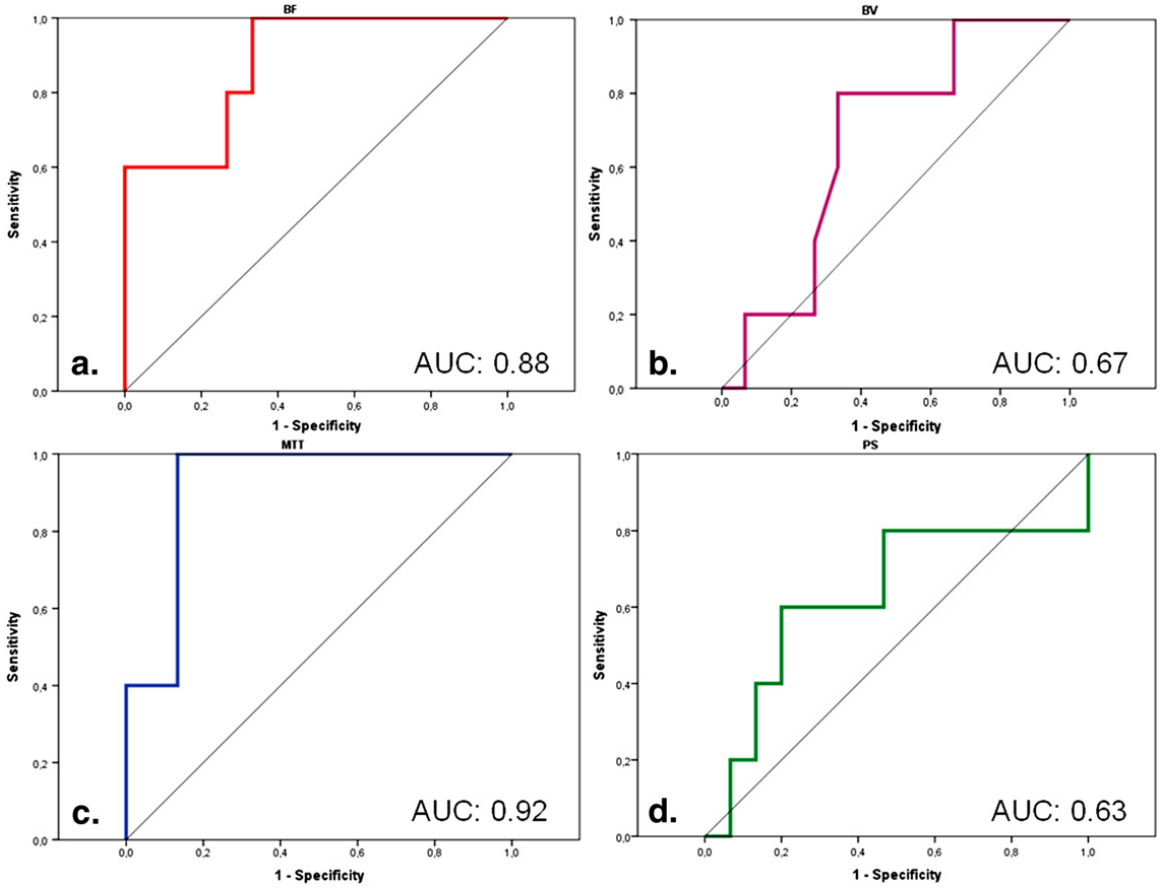


Figure VI.2. Comparison of receiver operating characteristic curves displaying the diagnostic performance for baseline measurements: (a) blood flow (BF); (b) blood volume (BV); (c) mean transit time (MTT); (d) permeability-surface area product (PS) in the evaluation of good response to chemoradiation therapy (tumor regression grades 3 and 4). AUC, area under the curve.

Corresponding sensitivities, specificities, PPV and NPV are provided in Table VI.2.

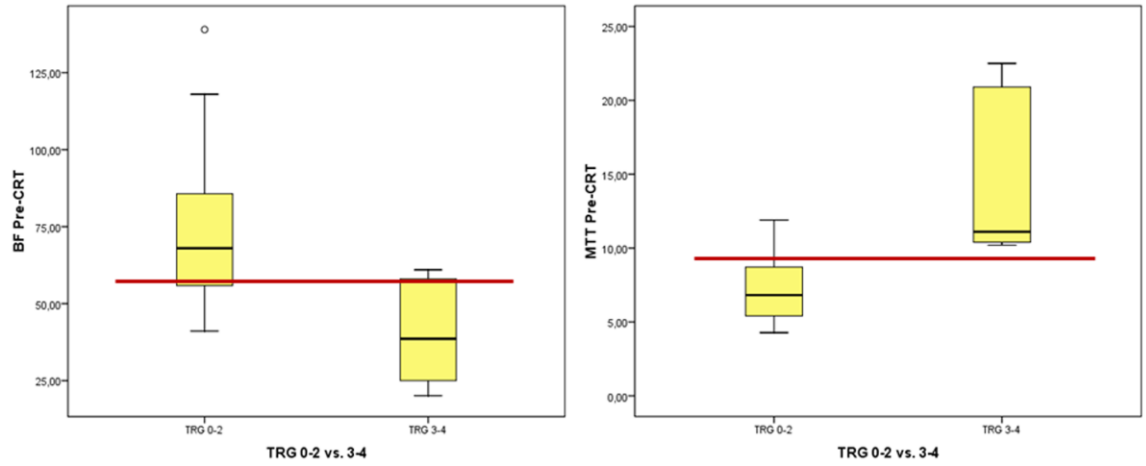
Perfusion Parameters	Sensitivity	Specificity	PPV	NPV	Cutoff Point
BF	80.0% [4/5] (28–99)	73.3% [11/15] (44–92)	50.0% [4/8] (15–84)	91.7% [11/12] (61–99)	59.25 mL/100 g/minute
BV	80.0% [4/5] (28–99)	66.7% [10/15] (38–88)	44.4% [4/9] (13–78)	90.9% [10/11] (58–99)	4.80 mL/100 g
MTT	100% [5/5] (47–100)	86.7% [13/15] (59–98)	71,4% [5/7] (29–96)	100% [13/13] (75–100)	9.52 seconds
PS	60.0% [3/5] (14–94)	80.0% [12/15] (51–95)	50.0% [3/6] (11–88)	85.7% [12/14] (57–98)	13.45 mL/100 g/minute

BF, blood flow; BV, blood volume; MTT, mean transit time; NPV, negative predictive value; PPV, positive predictive value; PS, permeability-surface area product.

Absolute numbers are given between brackets and 95% confidence intervals are provided between parentheses. Cutoff values were chosen according to the point nearest to the upper left corner in the receiver operating characteristic curves.

Table VI.2. Diagnostic performance of baseline perfusion measurements in detecting a good response to CRT.

Figure VI.3 shows box-and-whisker plots for BF and MTT, with depiction of the threshold value for discrimination between responders and non-responders.



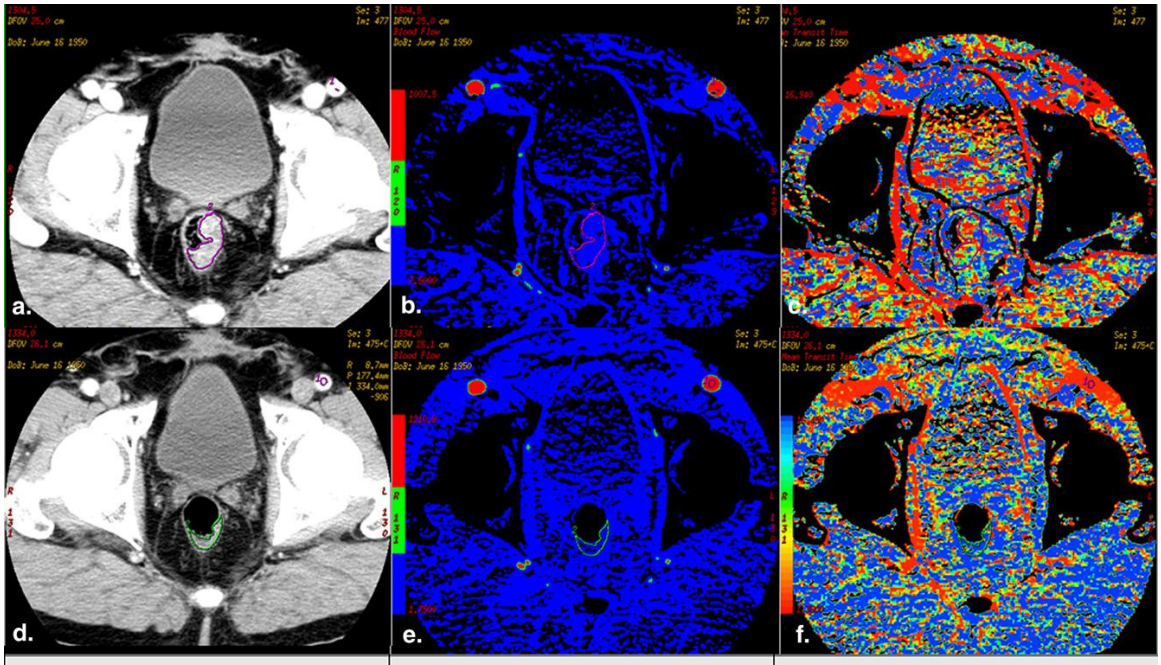
Perfusion parameters	Thresholds
BF (mL/100g/min)	59.25
MTT (s)	9.52

Figure VI.3. Box-and-whisker plots showing baseline blood flow (BF) and mean transit time (MTT) values of responders (tumor regression grade [TRG] 3-4) and nonresponders (TRG 0-2). Boxes stretch from lower quartile to upper quartile (25th to 75th percentile); median is shown as a line across each bar; whiskers show sample minimum and maximum; 0 denotes outliers; red horizontal lines represent thresholds. Using a threshold value of 59.25 mL/100 g/minute for BF it is possible to differentiate responders from nonresponders with a sensitivity of 80.0% and a specificity of 73.3%. Regarding MTT, a threshold of 9.52 seconds allows distinction between responders and nonresponders with a sensitivity of 100% and a specificity of 86.7%.

When both are taken in combination, they yield a sensitivity of 80% (95% CI: 28-99) and a specificity of 66.7% (95% CI: 38-88) for characterization of response.

3.6. Perfusion parameters before and after CRT

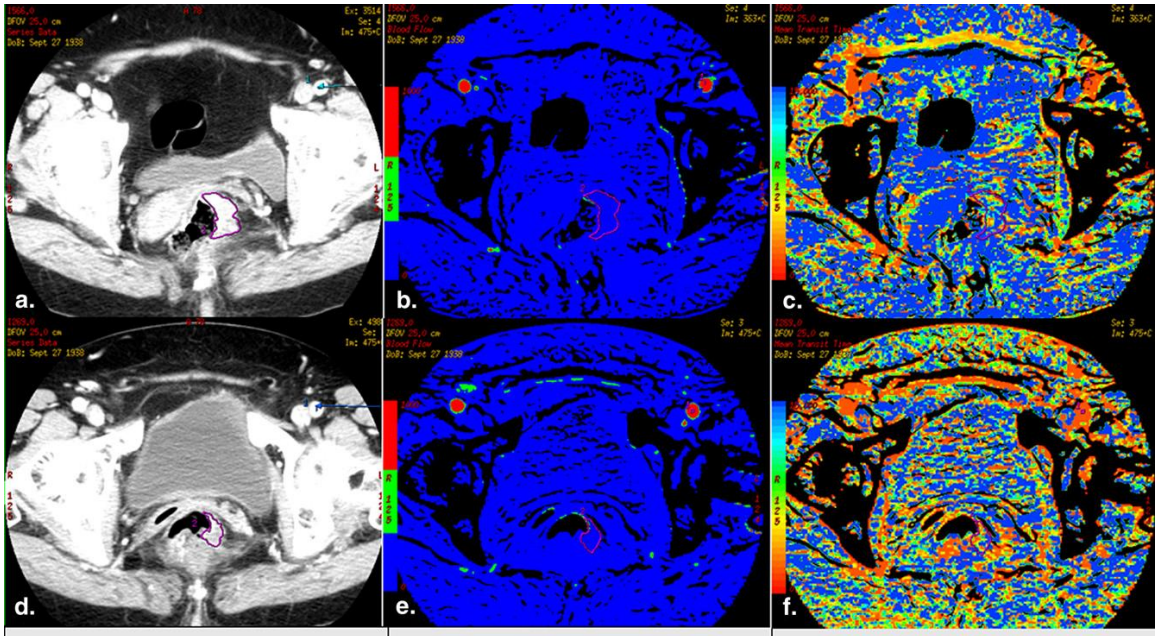
In the 11 patients who underwent pre- and post-CRT perfusion CT, the median BF on pre-CRT images was 61.00 mL/100g/min (range: 20.10–86.60) and on post-CRT CT was 20.10 mL/100g/min (range: 7.73–60.80) (*P*=0.003). For pre-CRT median BV was 4.84 mL/100g (range: 3.05–5.23) versus 2.80 mL/100g (range: 1.64–4.26) for post-CRT CT (*P*=0.003). The median MTT on pre-CRT scans was 8.63 s (range: 4.88–22.50) and on post-CRT images was 15.90 s (range: 4.48–26.70) (*P*=0.006). For pre-CRT CT, median PS was 12.80 mL/100g/min (range: 8.55–20.30) versus 9.51 mL/100g/min (range: 3.71–13.50) for post-CRT examination (*P*=0.008). Of these 11 patients, 4 were responders and 7 were non-responders. All responders and 4 non-responders showed lower BF, BV and PS and a higher MTT after CRT (Fig. VI.4).



Perfusion parameters	Baseline	Post-CRT
BF (mL/100g/min)	38.60	18.40
MTT (s)	10.40	19.90

Figure VI.4. Good responder to chemoradiation therapy (CRT): apart from morphological changes between pre- (a) and posttherapy (d) with a clear lesion downsizing, perfusion computed tomography showed a decrease in blood flow (BF) from pretreatment study (b) to posttreatment examination (e). There is also an increase in mean transit time (MTT): (c) baseline; (f) post-CRT. The blood volume and the permeability-surface area product (data and parametric maps not shown) also decreased.

Among non-responders, one showed higher BF and BV (Fig. VI.5), in other a higher PS was found and in a third the MTT was lower after CRT.



Perfusion parameters	Baseline	Post-CRT
BF (mL/100g/min)	79.30	61.20
MTT (s)	8.40	11.00

Figure VI.5. Poor responder to chemoradiation: absence of response to treatment was found with a lack of significant downsizing of the tumor between pre- (a) and posttherapy (d) images. Perfusion measurements revealed a decrease in the blood flow (BF): (b) baseline; (e) postchemoradiation therapy (CRT), and also in the mean transit time (MTT): (c) baseline; (f) post-CRT. The blood volume and the permeabilitysurface area product (data and parametric maps not shown) also decreased.

Nevertheless, the median variation rates of the perfusion parameters after CRT were not significantly different in responders and non-responders: 58.0% versus 63.0% (*P*=0.85) for BF, 29.1% versus 42.2% (*P*=0.70) for BV, 48.3% versus 84.2% (*P*=0.70) for MTT and 47.7% vs. 23.9% (*P*=0.13) for PS.

Table VI.3 yields a detailed view of the perfusion measurements on a patient-by-patient basis.

	BF (mL/100 g/mm^2)		BV (mL/100 g)		MTT (seconds)		PS (mL/100 g/mm^2)		
Patient Number	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT	TRG
1	86.60	20.20	4.86	2.00	4.88	13.00	18.00	13.50	1
2	84.80	23.60	5.08	1.85	6.15	11.00	8.55	8.99	2
3	38.60	18.40	4.65	3.21	11.10	21.00	20.30	7.89	3
4	51.30	19.00	5.23	2.24	8.63	16.00	12.50	9.51	2
5	41.10	60.80	3.05	3.38	8.80	9.70	10.90	7.20	2
6	65.20	9.22	5.05	3.05	8.33	27.00	16.60	11.10	2
7	79.30	52.90	4.84	2.80	5.62	4.50	12.80	11.90	1
8	25.00	9.08	3.58	2.61	22.50	24.00	13.70	9.00	3
9	68.00	53.00	4.21	3.50	5.19	9.90	11.40	11.10	1
10	20.10	20.10	4.28	4.26	20.90	23.00	11.90	11.80	4
11	47.80	NA	3.75	NA	8.83	NA	41.40	NA	2
12	79.70	NA	5.00	NA	6.82	NA	13.20	NA	2
13	60.50	NA	4.18	NA	7.24	NA	12.50	NA	2
14	118.00	NA	9.14	NA	5.72	NA	6.36	NA	2
15	109.00	NA	5.92	NA	5.02	NA	10.70	NA	1
16	50.00	NA	4.65	NA	11.90	NA	6.57	NA	0
17	139.00	NA	6.60	NA	4.28	NA	6.61	NA	0
18	58.00	NA	4.76	NA	10.20	NA	4.70	NA	3
19	63.70	NA	5.27	NA	11.50	NA	7.62	NA	2
20	61.00	7.73	5.17	1.64	10.40	20.00	17.70	3.71	4

BF, blood flow; BV, blood volume; CRT, chemoradiation therapy; MTT, mean transit time; NA, not applicable; PS, permeability-surface area product; TRG, tumor regression grade.

Table VI.3. Perfusion measurements on a patient-by-patient basis.

3.7. Radiation Dose

The effective radiation dose to the patients ranged from 36.03 mSv to 36.13 mSv. Of this, the cine acquisition was responsible for 20.74 mSv, while the remaining effective dose was related to the non-enhanced scans.

4. DISCUSSION

The results of our study show that baseline BF and MTT were significantly different in responders and non-responders (BF was significantly lower and MTT significantly higher in responders) and were accurate for predicting a favorable tumor response to CRT, with an AUC of 0.88 and 0.92, respectively. Baseline BV and PS were not significantly different among responders and non-responders. Comparing the functional perfusion data at baseline with those obtained following CRT conclusion, there was a significant change in all perfusion parameters: BF, BV and PS decreased while the MTT increased, but these changes were not different in responders and non-responders.

To our knowledge, assessing response to CRT as defined by the TRG has not been focused in previous studies of perfusion CT of rectal cancer. Former works addressed the diagnostic value of perfusion CT in evaluating response based on morphologic criteria of tumor downstaging [Bellomi et al, 2007; Sahani et al, 2005]. The use of these criteria as endpoint of response to CRT may be prone to under or overstaging and requires accurate baseline and post-CRT imaging examinations. However, our study assessed response to CRT based on the TRG, which is an objective criterion as standard of reference to evaluate response. Moreover, grade analysis is a better predictor of outcome after treatment than T downstaging [Bouzourene et al, 2002]. In patients with gross residual tumor (TRG 0–2), the risk of local and distant recurrence is increased and the disease-free survival is statistically poor [Losi et al, 2006].

Confirming the findings of a previous study [Sahani et al, 2005], our results showed that baseline BF and MTT are different between responders and non-responders, being respectively significantly higher and significantly lower in poorly-responding patients. This can be theoretically explained by the presence of intratumoral arteriovenous shunts with a high perfusion rate and low exchange of oxygen [Brown et al, 1998)]. Such arteriovenous shunts were shown to account for up to 30% of total tumor flow of blood [Eddy, 1980; Peters et al, 1980; Wheeler et al, 1986] and in an animal study it was demonstrated that tumoral areas of high BF in perfusion CT images corresponded to sites of shunting of blood flow [Kan et al, 2005]. These shunts have low resistance to flow, resulting in increased BF and shorter MTT. BV, although not significantly different, is also higher in poor responders. It seems therefore logical that high perfusion values, which suggest a high rate of angiogenesis within the tumor, may point towards a poor therapy response and/or a worse prognosis. High perfusion could also be a result of intrinsic high angiogenic activity of tumor [Leek et al, 1999]. Interestingly, our results disagree with those from a previous study that showed baseline BF and BV in poor responders to be significantly lower and MTT significantly higher than in responders [Bellomi et al, 2007]. Reason(s) for these discrepancies with our results may reflect not only the use of a different endpoint to assess response, different patient selection criteria (we did not use endorectal US for initial staging) and also differences in the perfusion technique: a shorter scanning time (effective scan duration of about 30 seconds) may be too short to reliably assess PS [Goh et al, 2005a; Miles, 2003], and use of thicker sections of 10 mm may also influence quantitative perfusion data [Bellomi et al, 2007]. Table VI.4 provides a comparison between the methods and findings of our study and those from the two above mentioned works.

Authors	Year	Number of Patients	Technical Parameters	Criteria for Response	Results	
					Prognostic Information	Monitoring of Treatment Response
Sahani et al	2005	15 (9 repeated after CRT)	4-row MDCT, 5-mm sections, 100–120 kVp, 200–240 mA, 125 mL of contrast (300 mg/mL), 45" acquisition	T downstaging at pathologic analysis compared with pre-CRT endorectal US or MRI	Cancers with high baseline BF and low MTT responded poorly to CRT	Fall in BF and rise in MTT after CRT
Bellomi et al	2007	25 (19 repeated after CRT)	16-row MDCT, 10-mm sections, 120 kVp, 300mA, 40 mL of contrast (370 mg/mL), 50" acquisition	T or N downstaging at pathologic analysis compared with pre-CRT endorectal US	Cancers with high baseline BF and BV showed good response to CRT	Fall in BF, BV, and PS after CRT
Curvo-Semedo et al	2011	20 (11 repeated after CRT)	64-row MDCT, 2.5-mm sections, 120 kVp, 300 mA, 100 mL of contrast (370 mg/mL), 60" acquisition	Dworak's TRG 3 or 4	Cancers with high baseline BF and low MTT responded poorly to CRT	Fall in BF, BV, and PS and rise in MTT after CRT

BF, blood flow; BV, blood volume; CRT, chemoradiation therapy; MDCT, multidetector computed tomography; MTT, mean transit time; PS, permeability-surface area product; TRG, tumor regression grade.

Table VI.4. Comparison of findings from previous reports on perfusion CT of rectal cancer with results from the present study.

Both baseline BF and MTT showed respectively AUCs of 0.88 and 0.92 in determining a good response to CRT, thus being able to yield a diagnostically useful threshold value. Therefore, BF values below 59.25 mL/100g/min and MTT values over 9.52 s were found to have high accuracy for predicting a good response to CRT. Contrarily, baseline BV and PS could not accurately discriminate responders from non-responders. Again, explanation for poor response is probably related to the opening of a significant number of arteriovenous shunts rather than the acquisition of a new vascular supply. Shunting facilitates the passage of blood directly from the arterial to the venous beds bypassing the exchange capillaries, hence decreasing MTT [Chaplin et al, 1997]. This would result in a high perfusion rate with minimal or null exchange of nutrients (including oxygen), therefore preventing and limiting the action of chemotherapeutic drugs over the capillary bed, helping to explain an unfavorable response [DeVries et al, 2001]. We are aware, however, that this explanation, which is also based on findings from previous reports [Kan et al, 2005; Sahani et al, 2005; Eddy, 1980, Peters et al, 1980, Wheeler et al, 1986, DeVries et al, 2001] is speculative, since it lacks pathologic confirmation. The previous studies on perfusion CT for monitoring CRT effects in rectal cancer showed significant changes in perfusion parameters after therapy. Sahani et al [2005] reported a significant decrease in BF and increase in MTT, whereas Bellomi et al [2007] showed a significantly lower BF, BV and PS after CRT. In agreement with those results, we demonstrated a significant change in perfusion parameters after CRT compared with the baseline scan: BF, BV and PS diminished, whereas MTT increased. This may reflect a decreased number of arteriovenous shunts (BF), a reduced volume of the vascular bed (BV) and a reduced leakage from neoplastic vessels (PS). The higher MTT is probably an expression of the sum of changes in the tumor vascular bed itself. However, the median variation rates of the perfusion parameters after CRT were not significantly different in responders and non-responders. Therefore, our results suggest that a baseline perfusion study alone could discriminate between responders and non-responders and a post-CRT is not warranted in order to achieve that goal.

Our study has limitations. Results are based on a small patient cohort of a single centre and are therefore specific to the methods and software we used, and as such our thresholds may not necessarily apply to other patients. They should be regarded as preliminary data that may stimulate studies on larger populations, especially multicenter trials encompassing standardization of protocols for perfusion CT in this clinical setting.

The use of a large (100 mL) dose of iodinated contrast is not recommended by some authors, who suggest that a smaller (<50 mL) bolus should be administered instead. Nevertheless, it was demonstrated that contrast volumes similar to those applied in clinical practice for abdominopelvic CT imaging are not detrimental to the accuracy of quantitative tumor vascular parameters measured at perfusion CT, with the advantage of obtaining simultaneously morphological (staging) data [Goh et al, 2009b]. Restrictions on the administration rates by the caliber of the iv cannula usually sited in clinical practice imply that rates above 5 mL/s are not commonly used [Goh et al, 2009b]. Moreover, the deconvolution method we applied can tolerate lower injection rates, such as less than 5 mL/s [Kambadakone et al, 2009]. The free-hand drawing of a ROI in a single slice may not fully represent the overall tumor vascular profile and implicates a subjective judgment by the readers of where the tumor margin is located. Therefore, even subtle variations in ROI size and positioning between readers may result in substantial variations in perfusion parameters. However, observer variability is lower for this type of ROI analysis as shown in other studies [Goh et al, 2005b; Goh et al, 2008a] and in concordance with our results with good to excellent interobserver agreement. We did not test

reproducibility, due to the radiation burden and concerns of contrast-induced nephropathy. A potentially distinct efficacy of the different chemotherapeutic drugs with impact on the results should theoretically be considered. We did not assess baseline tumor volume, which may predict response to therapy [Kim et al, 2005], nor did we evaluate changes in tumor volume after therapy, since contrast-enhanced scans of the whole pelvis were not performed. A direct correlation with histological markers of angiogenesis, such as microvessel density, was not performed since it is not routinely performed in our institution. Furthermore, there are limitations in its routine use as a biomarker: it requires invasive tissue sampling, needs standardization, and suffers from random sampling errors since the entire tumor volume is not examined, which can hamper evaluation because of the heterogeneity of malignant neoplasms [Cuénod et al, 2006].

5. CONCLUSION

In conclusion, baseline BF was significantly lower and MTT was significantly higher in responders than in non-responders and both parameters can accurately discriminate patients with a favorable response from the ones that fail to respond to preoperative CRT, potentially selecting high-risk patients with radio- and chemo-resistant tumors that may benefit from a more aggressive preoperative treatment approach.

Chapter VII

Summary and conclusions

1. SUMMARY

The present thesis focuses on the study of rectal cancer, which is one of the most frequently diagnosed neoplasms in the Western World, and is also associated with a high mortality rate. Long-term survival is highly dependent on tumor stage at discovery: tumors at an advanced stage at diagnosis are associated with a poor outcome. Accordingly, tumor stage at diagnosis is a guide to treatment strategies. As such, while patients with early cancers usually may achieve cure through surgery alone, those with locally advanced cancers typically undergo preoperative therapy, which is useful for decreasing the tumor stage in order to facilitate curative resection, and to decrease the local recurrence rate. Therefore, the role of the radiologist is to identify tumors within these groups, so that a tailored treatment can be offered to each single patient in order to decrease the probability of local recurrence.

In recent years, a paradigm shift toward less invasive treatments has been witnessed, including local excision by TEM or even a – still controversial – deferral from surgery in those patients achieving a complete response from the tumor following preoperative CRT.

However, no imaging techniques currently allow an accurate prediction of which tumors will respond satisfactorily to this kind of treatment, and which cases develop a complete response. This is particularly true when using purely morphological imaging methods, and consequently there has been a growing interest in more 'functional' imaging techniques, such as DW-MRI or perfusion CT.

Magnetic resonance imaging is widely used for the diagnosis and staging of tumors, whereby mainly morphometric macroscopic tissue information is usually obtained. For the assessment of viability and aggressiveness of the tumor or its response to therapy, a method that gives insights at a cellular level would be desirable. DW-MRI provides images whose signal intensity is sensitized to the random motion of free water molecules. The mobility of water molecules within a given voxel is determined by the microscopic cellular structure, i.e., the presence of barriers, such as cell membranes and macromolecules. Thus, DWI has been suggested as a tool to distinguish different tissue compartments based on their different cellular structure. As such, this method offers a theoretical possibility for the assessment of viability of the tumor or its response to therapy.

Perfusion CT is a technology that allows measurement of tumor vascular physiology and construction of regional maps of tumor blood flow, blood volume, mean transit time, and vascular permeability–surface area product. This type of study can be repeated at different times to assess tumor response to temporal changes in tumor angiogenesis or anti-angiogenic therapy.

The contribution of this study focuses mainly on the aforementioned 'functional' techniques. I attempted to bring a new insight into their use in the study of rectal cancer and also to give an own contribution to the consolidation of their routine application in everyday clinical practice. It was possible to demonstrate that both techniques, despite not being ready to fulfil that role yet, may be valuable in characterizing rectal tumors and may provide additional information about response and prognosis.

Diffusion-weighted imaging has the potential to become an imaging biomarker in these tumors, as lower ADCs are found in more aggressive tumors. DWI-based volumetry can help in predicting response to neoadjuvant therapy and assessing the presence of complete tumoral response. Perfusion CT can also aid in the prediction of response, as tumors with lower blood flow may respond more favourably to neoadjuvant combined chemoradiation therapy.

2. CONCLUSIONS

1. Significant correlations between ADC values and the clinical MRF status, and nodal status on MR imaging and the tumor differentiation grade at histology have been statistically demonstrated. There is a tendency towards lower ADC values in tumors with involvement of the MRF, node-positive tumors, poorly differentiated neoplasms, lesions growing beyond the rectal wall, CEA levels higher or equal to than 5 ng/mL, and tumors with LVI, which are the cancers with poorer prognosis. This study suggests that ADC has the potential to become an imaging biomarker of tumor biological profile.

2. It was also proved that tumor volumetry performed on DW MR images after combined CRT assesses complete tumor response accurately, and is significantly more accurate than volumetry performed on post-CRT T2-w MR images. Tumor volume reduction measurements performed on either T2-w MR images or DW MR images are equally as accurate as measurements performed on post-CRT DW MR images in assessing a CR. Tumor volumes measured on either pre-CRT T2-w MR images or pre-CRT DW MR images are not accurate for the assessment of a CR. ADC measurements do not assess a CR accurately. This way, tumor volumetry performed on post-CRT DW MR images may be used for the clinical selection of rectal cancer patients with a CR after CRT who might be stratified for conservative, non-surgical follow-up treatment.

3. When measuring ADC in patients with locally advanced rectal cancer, ADC values and interobserver variability are highly dependent on the methods of ROI analysis. The most reproducible results derive from ADC measurements of the whole tumor volume. Tumor ADC measurements are more reproducible before rather than after chemoradiation treatment. In specific, the ROI size and positioning influence tumor ADC measurements in rectal cancer, as well as interobserver variability of tumor ADC measurements. As such, variations caused by ROI size and positioning should be taken into account when using ADC as a biomarker for tumor response.

4. A significant difference in perfusion parameters of rectal cancers in responders and non-responders as determined by perfusion CT has been shown. In specific, BF was significantly lower and MTT significantly higher in responders, and both have proved to be accurate for predicting a favorable tumor response to CRT. Comparing the functional perfusion data at baseline with those obtained following CRT conclusion, there was a significant change in all perfusion parameters: BF, BV and PS decreased while the MTT increased, but these changes were not different in responders and non-responders. Therefore, perfusion CT may help to select high-risk patients with radio- and chemo-resistant tumors that may benefit from a more aggressive preoperative treatment approach.

SUMÁRIO

Na presente tese focamo-nos no estudo do cancro do recto, que constitui uma das neoplasias mais frequentemente diagnosticadas nos países desenvolvidos, associada a uma elevada taxa de mortalidade. A sobrevivência dos pacientes encontra-se intimamente relacionada com o estádio do tumor aquando do diagnóstico: lesões num estádio mais avançado associam-se a um prognóstico mais sombrio. Por seu turno, o estadiamento tumoral constitui a base para a tomada de decisões terapêuticas e, desta forma, pacientes com tumores em estádios mais precoces podem ser curados através de cirurgia, enquanto que aqueles com tumores localmente avançados são via de regra submetidos a terapêutica pré-operatória com o intuito de promover o 'downstaging' tumoral e dessa forma facilitar a ressecção cirúrgica com intenção curativa, bem como diminuir a taxa de recidiva local. Consequentemente, o papel do radiologista consiste em classificar as lesões nestes grupos, de forma que o tratamento possa ser ajustado e individualizado para cada paciente no sentido de reduzir a probabilidade de surgir uma recidiva local.

Recentemente temos vindo a testemunhar uma alteração no paradigma terapêutico desta patologia, com o aparecimento de tratamentos minimamente invasivos, incluindo a excisão local transanal ou mesmo um adiamento da cirurgia com vigilância regular e periódica naqueles doentes em que se consegue obter uma resposta tumoral completa após terapêutica neoadjuvante com radio- e quimioterapia combinadas (embora tal abordagem seja ainda objecto de considerável controvérsia).

Contudo, no presente momento as técnicas de imagem não permitem seleccionar com acuidade suficiente quais os tumores que irão responder de forma satisfatória a este tipo de tratamento nem quais os casos que atingirão uma eventual resposta completa. Estas afirmações são particularmente verdadeiras se considerarmos os métodos de imagem puramente morfológicos, pelo que se tem verificado um interesse crescente por técnicas de imagem mais 'funcionais', como sejam a difusão por Ressonância Magnética e a perfusão por Tomografia Computorizada.

A Ressonância Magnética é amplamente utilizada no diagnóstico e estadiamento de tumores, fornecendo essencialmente informação morfológica macroscópica acerca dos tecidos. Para avaliação da agressividade e viabilidade do tumor ou da sua resposta à terapêutica, tornar-se-á necessário recorrer a métodos que forneçam informação sobre as características do tumor a nível celular. A intensidade de sinal das estruturas nas imagens de Ressonância Magnética ponderadas em difusão dependem da amplitude do movimento aleatório das moléculas de água, cuja mobilidade em cada voxel é determinada pela estrutura celular microscópica, isto é, pela presença de barreiras que restringem o movimento, como membranas celulares e macromoléculas. Assim sendo, a difusão por Ressonância Magnética pode tornar-se uma ferramenta útil na distinção de diferentes compartimentos teciduais baseando-se na sua distinta estrutura celular, teoricamente oferecendo a possibilidade de avaliar a viabilidade de um tumor e também o seu grau de resposta à terapêutica.

A perfusão por Tomografia Computorizada é uma tecnologia que permite a avaliação da fisiologia vascular do tumor e a obtenção de mapas paramétricos de côr do fluxo sanguíneo, volume sanguíneo, tempo de trânsito médio e produto permeabilidade-superfície vascular. Este estudo pode facilmente ser repetido em diferentes tempos para avaliar a resposta do tumor e as alterações da sua angiogénese.

A nossa contribuição pessoal centrou-se principalmente em estudos referentes às técnicas de imagem 'funcionais' acima mencionadas. Ao fazê-lo, procurámos reforçar o seu papel no estudo do cancro do recto e também, de uma forma despretensiosa, oferecer o nosso próprio contributo para a consolidação do seu uso rotineiro na prática clínica diária no futuro.

Foi-nos possível demonstrar que ambas as técnicas supra citadas, apesar de, em nosso entender, ainda incapazes de cumprir tal desiderato, podem desempenhar um relevante papel na caracterização dos tumores rectais e fornecer informação adicional acerca do grau de resposta tumoral e do prognóstico dos doentes.
A difusão por Ressonância Magnética tem potencial para se tornar um biomarcador imagiológico destes tumores, pois ADCs mais baixos encontram-se associados a tumores mais agressivos. A volumetria tumoral efectuada com base nas imagens ponderadas em difusão pode auxiliar a prever a resposta tumoral à terapêutica neoadjuvante e a presença de uma resposta tumoral completa.
A perfusão por Tomografia Computorizada pode de idêntica forma auxiliar na previsão da resposta, decorrendo do facto de tumores com menor fluxo sanguíneo responderem mais favoravelmente à terapêutica neoajduvante combinada com radio- e quimioterapia.

CONCLUSÕES

Demonstrámos correlações estatisticamente significativas entre os valores de ADC e o estado da fáscia mesorrectal e o estadiamento ganglionar na RM e o grau de diferenciação tumoral na histologia. Houve uma tendência no sentido de encontrar valores de ADC mais baixos em tumores com invasão da fáscia mesorrectal, na doença metastática ganglionar, em lesões histologicamente pouco diferenciadas, em neoplasias com crescimento extra-parietal, em casos de doseamentos de CEA iguais ou superiores a 5 ng/mL, e em tumores com invasão linfangiovascular, aspectos estes associados a lesões com um prognóstico mais sombrio. O nosso estudo sugere que o ADC revela potencial para se tornar um biomarcador imagiológico do perfil biológico dos cancros do recto.

Provámos que a volumetria tumoral efectuada com base nas imagens ponderadas em difusão após o tratamento combinado com radio- e quimioterapia possui uma elevada acuidade na avaliação da resposta tumoral completa e significativamente superior à da volumetria baseada nas imagens pós-terapêutica ponderadas em T2. A mensuração da redução do volume tumoral efectuada nas imagens ponderadas em T2 ou nas imagens ponderadas em difusão revela idêntica acuidade à da volumetria baseada nas imagens pós- terapêutica ponderadas em difusão na avaliação da resposta tumoral completa. A volumetria tumoral efectuada com base nas imagens pré-terapêutica ponderadas em T2 ou em difusão revelou uma baixa acuidade na determinação de uma resposta tumoral completa. Desta forma, a volumetria tumoral baseada nas imagens pós-terapêutica ponderadas em difusão pode ser aplicável na selecção clínica de pacientes com cancro do recto com uma resposta tumoral completa após tratamento combinado de radio- e quimioterapia, que podem dessa forma ser sujeitos a uma abordagem mais conservadora, não cirúrgica, através uma regular vigilância clínica, endoscópica e imagiológica.

Concluímos que na mensuração dos valores de ADC em pacientes com cancros do recto localmente avançados, esses mesmos valores e a variabilidade são altamente dependentes dos métodos de análise das regiões de interesse. Especificamente, o tamanho da região de interesse e o seu posicionamento sobre o tumor influenciam os valores de ADC tumoral e a variabilidade interobservador. Os resultados com maior reprodutibilidade derivam das mensurações efectuadas para todo o volume tumoral. A determinação dos valores de ADC é também mais reprodutível antes do que depois do tratamento pré-cirúrgico com uma combinação de radio- e quimioterapia. Como tal, as variações causadas pelas dimensões e posicionamento das regiões de interesse devem ser consideradas aquando da determinação dos valores de ADC.

Encontrámos uma diferença significativa nos valores dos parâmetros de perfusão nos cancros do recto que mostraram boa resposta à radioquimioterapia relativamente àqueles que responderam de forma pouco satisfatória. Concretamente, o fluxo sanguíneo foi significativamente menor e o tempo de trânsito médio foi significativamente mais elevado nos tumores com uma boa resposta, e estes parâmetros provaram possuir elevada acuidade na determinação de uma resposta favorável à radioquimioterapia neoadjuvante. Comparando os dados basais com os obtidos após conclusão da radioquimioterapia, houve uma alteração significativa em todos os parâmetros de perfusão: o fluxo sanguíneo, o volume sanguíneo e o produto permeabilidade-superfície vascular decresceram, enquanto que o tempo de trânsito médio aumentou. No entanto, estas diferenças não foram estatisticamente significativas entre neoplasias com um distinto grau de resposta. Desta forma, a perfusão por Tomografia Computorizada pode auxiliar a selecção de doentes com elevado risco de recidiva, possuidores de tumores radio- e/ou quimiorresistentes e que podem beneficiar de uma abordagem terapêutica pré-cirúrgica mais agressiva.

List of Publications

1. Diffusion-weighted MRI in rectal cancer: Apparent diffusion coefficient as a potential noninvasive marker of tumor aggressiveness.
***Curvo-Semedo L**, Lambregts DM, Maas M, Beets GL, Caseiro-Alves F, Beets-Tan RG.*
J Magn Reson Imaging. 2012 Jun;35(6):1365-71. doi: 10.1002/jmri.23589. Epub 2012 Jan 23.

2. Rectal cancer: assessment of complete response to preoperative combined radiation therapy with chemotherapy-conventional MR volumetry versus diffusion-weighted MR imaging.
***Curvo-Semedo L**, Lambregts DM, Maas M, Thywissen T, Mehsen RT, Lammering G, Beets GL, Caseiro-Alves F, Beets-Tan RG.*
Radiology. 2011 Sep;260(3):734-43. Epub 2011 Jun 14. PMID: 21673229

3. Tumour ADC measurements in rectal cancer: effect of ROI methods on ADC values and interobserver variability.
*Lambregts DM, Beets GL, Maas M, **Curvo-Semedo L**, Kessels AG, Thywissen T, Beets-Tan RG.*
Eur Radiol. 2011 Dec;21(12):2567-74. Epub 2011 Aug 7. PMID: 21822946

4. Usefulness of perfusion CT to assess response to neoadjuvant combined chemoradiotherapy in patients with locally advanced rectal cancer.
***Curvo-Semedo L**, Portilha MA, Ruivo C, Borrego M, Leite JS, Caseiro-Alves F.*
Acad Radiol. 2012 Feb;19(2):203-13. Epub 2011 Nov 30. PMID: 22130088

References

- Abdel-Nabi H, Doerr RJ, Lamonica DM, et al. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. Radiology 1998;206:755–760.
- Abir F, Alva S, Longo WE, et al. The postoperative surveillance of patients with colon cancer and rectal cancer. Am J Surg 2006;192:100–108.
- Abulafi AM, Williams NS. Local recurrence of colorectal cancer: the problem, mechanisms, management and adjuvant therapy. Br J Surg 1994;81:7–19.
- ACPGB2I. Guidelines for the management of colorectal cancer. Issued by the Association of Coloproctology of Great Britain and Ireland. www.acpgbi.org.uk.
- Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994;344:707–711.
- Ahlquist DA, Shuber AP. Stool screening for colorectal cancer: evolution from occult blood to molecular markers. Clin Chim Acta 2002;315:157-168.
- Ahsan H, Neugut AI, Garbowski GC, et al. Family history of colorectal adenomatous polyps and increased risk for colorectal cancer. Ann Intern Med 1998;128(11):900-905.
- Akasu T, Sugihara K, Moriya Y, Fujita S. Limitations and pitfalls of transrectal ultrasonography for staging of rectal cancer. Dis Colon Rectum 1997;40(suppl):S10–S15.
- Akasu T, Kondo H, Moriya Y, et al. Endorectal ultrasonography and treatment of early stage rectal cancer. World J Surg 2000;24:1061–1068.
- Akasu T, Iinuma G, Fujita T et al. Thin-section MRI with a phased-array coil for preoperative evaluation of pelvic anatomy and tumor extent in patients with rectal cancer. AJR Am J Roentgenol 2005;184:531–538.
- Akhurst T, Larson SM. Positron emission tomography imaging of colorectal cancer. Semin Oncol 1999;26:577–583.
- Alberts DS, Martínez ME, Roe DJ, et al. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. N Engl J Med 2000;342(16):1156-1162.
- Allen SD, Padhani AR, Dzik-Jurasz AS, Glynne-Jones R. Rectal carcinoma: MRI with histologic correlation before and after chemoradiation therapy. AJR Am J Roentgenol 2007;188(2):442–451.
- Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.
- Andreola S, Leo E, Belli F, et al. Manual dissection of adenocarcinoma of the lower third of the rectum specimens for detection of lymph node metastases smaller than 5 mm. Cancer 1996;77:607–612.
- Angelelli G, Macarini L, Lupo L. Rectal carcinoma: CT staging with water as contrast medium. Radiology 1990;177:511–514.
- Anzai Y, Prince M. Iron oxide-enhanced MR lymphography: the evaluation of cervical lymph node metastases in head and neck cancer. J Magn Reson Imaging 1997;7:75-81.
- Arriola E, Navarro M, Pares D, et al. Imaging techniques contribute to increased surgical rescue of relapse in the follow-up of colorectal cancer. Dis Colon Rectum 2006;49:478–484.
- Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl I Med 1992;326:658-662.
- Atkin WS, Cuzick I, Northover IM, Whynes DK. Prevention of colorectal cancer by once-only sigmoidoscopy. Lancet 1993;341(8847):736-740.

- Balch GC, De Meo A, Guillem JG. Modern management of rectal cancer: a 2006 update. World J Gastroenterol 2006;12:3186–3195.
- Bammer R. Basic principles of diffusion-weighted imaging. Eur J Radiol.2003;45:169–184.
- Barbaro B, Fiorucci C, Tebala C, et al. Locally advanced rectal cancer: MR imaging in prediction of response after preoperative chemotherapy and radiation therapy. Radiology 2009;250:730–739.
- Barbaro B, Vitale R, Leccisotti L, et al. Restaging locally advanced rectal cancer with MR imaging after chemoradiation therapy. RadioGraphics 2010;30(3):699–716.
- Barillari P, Ramacciato G, Manetti G, et al. Surveillance of colorectal cancer: effectiveness of early detection of intraluminal recurrences on prognosis and survival of patients treated for cure. Dis Colon Rectum 1996;39:388-393.
- Barrett MW. Chemoradiation for rectal cancer: current methods. Semin Surg Oncol 1998;15:114–119.

- Becker CD, Fuchs WA. Colorectal carcinoma. In: Meyers MA (ed) Computed tomography of the gastrointestinal tract. Springer; Berlin Heidelberg New York, 1986.
- Beets-Tan RG, Beets GL, van der Hoop AG, et al. High-resolution magnetic resonance imaging of the anorectal region without an endocoil. Abdom Imaging 1999;24:576–581;discussion 582–584.
- Beets-Tan RG, Beets GL, Borstlap AC, et al. Preoperative assessment of local tumor extent in advanced rectal cancer: CT or high-resolution MRI? Abdom Imaging 2000;25:533–541.
- Beets-Tan RG, Beets GL, Vliegen RF, et al. Accuracy of magnetic resonance imaging in prediction of tumor-free resection margin in rectal cancer surgery. Lancet 2001a;357:497–504.
- Beets-Tan RG, Morren GL, Beets GL, et al. Measurement of anal sphincter muscles: endoanal US, endoanal MR imaging, or phased-array MR imaging?—a study with healthy volunteers. Radiology 2001b;220:81–89.
- Beets-Tan RG, Beets GL, van der Hoop AG, et al. Preoperative MR imaging of anal fistulas: does it really help the surgeon? Radiology 2001c;218:75–84.
- Beets-Tan RG, Beets GL. Rectal cancer: review with emphasis on MR imaging. Radiology 2004;232:335–346.
- Beets-Tan RG, Beets G. Local Staging of Rectal Cancer: A Review of Imaging. J. Magn Reson Imaging 2011;33:1012–1019.
- Bellomi M, Petralia G, Sonzogni A, Zampino MG, Rocca A. CT Perfusion for the Monitoring of Neoadjuvant Chemotherapy and Radiation Therapy in Rectal Carcinoma: Initial Experience. Radiology 2007;244:486-493.
- Beynon J, Foy DM, Roe AM, Temple LN, Mortensen NJ. Endoluminal ultrasound in the assessment of local invasion in rectal cancer. Br J Surg 1986;73:474–477.
- Billingham RP. Extended lymphadenectomy for rectal cancer: cure vs quality of life. Int Surg 1994;79:11–22.
- Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MRI—a meta-analysis. Radiology 2004;232:773–783.
- Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 2002;235:449–457.
- Birgisson H, Pahlman L, Gunnarsson U, et al: Adverse effects of preoperative radiation therapy for rectal cancer: Long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol 2005;23:8697-8705.
- Bissett IP, Fernando CC, Hough DM, et al: Identification of the fascia propria by magnetic resonance imaging and its relevance to preoperative assessment of rectal cancer. Dis Colon Rectum 2001;44:259–265.
- Bjelovic M, Kalezic V, Petrovic M, et al. Correlation of macroscopic and histological characteristics in the regional lymph nodes of patients with rectal and sigmoidal adenocarcinoma. Hepatogastroenterology 1998;45:433–438.
- Blair S, Ellenhorn JD. Transanal excision for low rectal cancers is curative in early-stage disease with favorable histology. Am Surg 2000;66:817–820.
- Blomqvist L, Holm T, Goranson H et al. MR imaging, CT and CEA scintigraphy in diagnosis of local recurrence of rectal cancer. Acta Radiol 1996;37:779–784.
- Blomqvist L, Holm T, Rubio C, Hindmarsh T. Rectal tumors: MR imaging with endorectal and/or phased-array coils, and histopathological staging on giant sections—a comparative study. Acta Radiol 1997;38:437–444.
- Blomqvist L, Fransson P, Hindmarsh T. The pelvis after surgery and radio-chemotherapy for rectal cancer studied with Gd-DTPA-enhanced fast dynamic MR imaging. Eur Radiol 1998;8:781–787.
- Blomqvist L, Rubio C, Holm T, Machado M, Hindmarsh T. Rectal adenocarcinoma: assessment of tumour involvement of the lateral resection margin by MRI of resected specimen. Br J Radiol 1999;72(853):18–23.
- Blomqvist L, Machado M, Rubio C, et al. Rectal tumor staging: MR imaging using pelvic phased-array and endorectal coils vs endoscopic ultrasonography. Eur Radiol 2000;10:653–660.
- Bokemeyer C, Bondarenko I, Makhson A, et al: Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27:663-671.
- Bokey EL, Ojerskog B, Chapuis P, Dent O, Newland RC, Sinclair G. Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: Role of total anatomical dissection. Br J Surg 1999;86:1164-1170.
- Bond JH. Progress in refining virtual colonoscopy for colorectal cancer screening. Gastroenterology 2005;129(6):2103-2106.

- Borschitz T, Wachtlin D, Möhler M, et al. Neoadjuvant chemoradiation and local excision for T2–3 rectal cancer. Ann Surg Oncol 2008;15:712–720.
- Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-1123.
- Bostick RM, Fosdick L, Wood JR, et al. Calcium and colorectal epithelial cell proliferation in sporadic adenoma patients: a randomized, double-blinded, placebo-controlled clinical trial. J Natl Cancer Inst 1995;87(17):1307-1315.
- Bouzourene H, Bosman FT, Seelentag W, Matter M, Coucke P. Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2002;94:1121–1130.
- Bozzetto F, Baratti D, Andreola S, et al. Preoperative radiation therapy for patients with T2–T3 carcinoma of the middle-to-lower rectum. Cancer 1999;86:398–404.
- Brasch RC, Li KC, Husband JE, et al. In vivo monitoring of tumour angiogenesis with MR imaging. Acad Radiol 2000;7(10):812–823.
- Brown CL, Ternent CA, Thorson AG, et al. Response to preoperative chemoradiation in stage II and III rectal cancer. Dis Colon Rectum 2003;46:1189–1193.
- Brown G, Richards CJ, Newcombe RG, et al. Rectal carcinoma: thin section MRI for staging in 28 patients. Radiology 1999;211:215–222.
- Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg 2003a;90:355–364.
- Brown G, Richards CJ, Bourne MW, et al. Morphologic predictors of lymph node status in rectal cancer with use of high spatial resolution MRI with histopathologic comparison. Radiology 2003b;227:371–377.
- Brown G, Daniels IR. Preoperative staging of rectal cancer: The MERCURY research project. Recent Results Cancer Res 2005;165:58-74.
- Brown H: Thin section MRI in multidisciplinary pre-operative decision making for patients with rectal cancer. Br J Radiol 2005;78:S117–S127.
- Brown JM, Giaccia AJ. The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. Cancer Res 1998;58:1408–1416.
- Bruegel M, Holzapfel K, Gaa J, et al. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. Eur Radiol 2008;18:477–485.
- Bujko K, Kepka L, Nowacki MP. Chemoradiotherapy alone for rectal cancer: a word of caution [letter]. Lancet Oncol 2007;8(10):860–862.
- Burling D, Halligan S, Slater A, Noakes MJ, Taylor SA. Potentially serious adverse events at CT colonography in symptomatic patients: national survey of the United Kingdom. Radiology 2006;239(2):464-471.
- Burnstein MJ. Dietary factors related to colorectal neoplasms. Surg Clin North Am. 1993;73(1):13-29.
- Burt RW, Bishop DT, Cannon LA, Dowdle MA, Lee RG, Skolnick MH. Dominant inheritance of adenomatous colonic polyps and colorectal cancer. N Engl J Med 1985;312(24):1540-1544.
- Butch RJ, Stark DD, Wittenberg J, et al. Staging rectal cancer by MR and CT. AJR Am J Roentgenol 1986;146:1155–1160.

- Caderni G, Palli D, Lancioni L, et al. Dietary determinants of colorectal proliferation in the normal mucosa of subjects with previous colon adenomas. Cancer Epidemiol Biomarkers Prev 1999;8(3):219-225.
- Calvo FA, Domper M, Matute R, et al. ^{18}F-FDG positron emission tomography staging and restaging in rectal cancer treated with preoperative chemoradiation. Int J Radiat Oncol Biol Phys 2004;58:528–535.
- Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on the quality of life. Eur J Surg Oncol 2001;27:349–353.
- Cammà C, Giunta M, Fiorica F, et al. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. JAMA 2000;284:1008–1015.
- Capirci C, Rubello D, Chierichetti F, et al. Restaging after neoadjuvant chemoradiotherapy for rectal adenocarcinoma: role of F^{18}-FDG PET. Biomed Pharmacother 2004;58:451–457.
- Carrington B. Lymph nodes. In: Husband JES, Reznek RH (eds.) Imaging in oncology. Dunitz; Oxford, England, 1998.

- Cascini GL, Avallone A, Delrio P, et al. ^{18}F-FDG-PET is an early predictor of pathologic tumor response to preoperative radiochemotherapy in locally advanced rectal cancer. J Nucl Med. 2006;47:1241–1248.
- Cawthorn SJ, Parums DV, Gibbs NM, et al. Extent of mesorectal spread and involvement of lateral resection margin as prognostic factors after surgery for rectal cancer. Lancet 1990;335:1055–1059.
- Chan TW, Kressel HY, Milestone B, et al. Rectal carcinoma: staging at MR imaging with endorectal surface coil—work in progress. Radiology 1991;181:461–467.
- Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA, Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99(6):433–441.
- Chaplin DJ, Trotter MJ, Dougherty GJ. Microregional tumor blood flow: heterogeneity and therapeutic significance. In Bicknell R, Lewis CE, Ferrara N (eds.) Tumor angiogenesis. Oxford University Press; Oxford, England, 1997.
- Chapuis PH, Dent OF, Fisher R, et al. A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. Br J Surg 1985;72:698-702.
- Chau I, Allen M, Cunningham D, et al. Neoadjuvant systemic fluorouracil and mitomycin C prior to synchronous chemoradiation is an effective strategy in locally advanced rectal cancer. Br J Cancer 2003;88:1017-1024.
- Chen J, Stampfer MJ, Hough HL, et al. A prospective study of N-acetyltransferase genotype, red meat intake, and risk of colorectal cancer. Cancer Res 1998;58(15):3307-3311.
- Chen CC, Lee RC, Lin JK, Wang LW, Yang SH. How accurate is magnetic resonance imaging in restaging rectal cancer in patients receiving preoperative combined chemoradiotherapy? Dis Colon Rectum 2005;48(4):722–728.
- Chenevert TL, McKeever PE, Ross BD. Monitoring early response of experimental brain tumors to therapy using diffusion magnetic resonance imaging. Clin Cancer Res 1997;3(9):1457–1466.
- Chiesura-Corona M, Muzzio PC, Giust G, Zuliani M, Pucciarelli S, Toppan P. Rectal cancer: CT local staging with histopathologic correlation. Abdom Imaging 2001;26:134–138.
- Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: A phase 2 trial. Lancet Oncol 2010;11:241-248.
- Chung CK, Stryker JA, Demuth WE. Patterns of failure following surgery alone for colorectal carcinoma. J Surg Oncol 1983;22:65–70.
- Chung DC, Rustgi AK. The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. Ann Intern Med 2003;138(7):560-570.
- Church TR. A novel form of ascertainment bias in case-control studies of cancer screening. J Clin Epidemiol 1999;52:837-847.
- Coco C, Manno A, Mattana C, et al. The role of local excision in rectal cancer after complete response to neoadjuvant treatment. Surg Oncol 2007;16(suppl 1):S101–S104.
- Colquhoun PH, Wexner SD. Surgical management of colon cancer. Curr Gastroenterol Rep 2002;4(5):414-419.
- Collette L, Bosset JF, den Dulk M, et al: Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: Does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organization for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol 2007;25:4379-4386.
- Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001;358:1291–1304.
- Cova M, Frezza F, Pozzi-Mucelli RS, et al. Computed tomography and magnetic resonance in the preoperative staging of the spread of rectal cancer: a correlation with the anatomicopathological aspects. Radiol Med (Torino) 1994;87:82–89.
- Crane CH, Eng C, Feig BW, et al: Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2010;76:824-830.
- Cuénod CA, Fournier L, Balvay D, et al. Tumor angiogenesis: pathophysiology and implications for contrast-enhanced MRI and CT assessment. Abdom Imaging 2006;31(2):188–193.
- Cui Y, Zhang XP, Sun YS, Tang L, Shen L. Apparent diffusion coefficient: potential imaging biomarker for prediction and early detection of response to chemotherapy in hepatic metastases. Radiology 2008;248:894–900.
- Cunningham D, Humblet Y, Siena S, et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.

- de Haas-Kock DF, Baeten CG, Jager JJ et al. Prognostic significance of radial margins of clearance in rectal cancer. Br J Surg 1996;83:781–785.
- de Lange EE, Fechner RE, Wanebo HJ. Suspected recurrent rectosigmoid carcinoma after abdominoperineal resection: MR imaging and histopathologic findings. Radiology 1989;170:323–328.
- de Lange EE, Fechner RE, Edge SB, Spaulding CA. Preoperative staging of rectal carcinoma with MR imaging: surgical and histopathologic correlation. Radiology 1990;176(3):623–628.
- Delbeke D, Walker RC. Colorectal cancer. In: Delbeke D, Israel O (eds.) Hybrid PET/CT and SPECT/CT Imaging. Springer; Heidelberg, Germany, 2010.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(3):837–845.
- Desch CE, Benson AB 3rd, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American society of clinical oncology practice guideline. J Clin Oncol 2005;23:8512–8519.
- DeSouza NM, Hall AS, Puni R, Gilderdale DJ, Young IR, Kmiot WA. High resolution magnetic resonance imaging of the anal sphincter using a dedicated endoanal coil: comparison of magnetic resonance imaging with surgical findings. Dis Colon Rectum 1996;39:926–934.
- DeSouza NM, Riches SF, VanAs NJ et al. Diffusion-weighted magnetic resonance imaging: a potential non-invasive marker of tumour aggressiveness in localized prostate cancer. Clin Radiol 2008:63(7):774-82.
- DeVries AF, Griebel J, Kremser C et al. Tumor Microcirculation Evaluated by Dynamic Magnetic Resonance Imaging Predicts Therapy Outcome for Primary Rectal Carcinoma. Cancer Res 2001;61:2513-2516.
- DeVries AF, Kremser C, Hein PA, et al. Tumor Microcirculation and Diffusion Predict Therapy Outcome for Primary Rectal Carcinoma. Int J Radiation Oncology Biol Phys 2003;56:958–965.
- Dewdney A, Cunningham D, Tabernero J, et al. EXPERT-C: A randomized phase II European multicenter trial of neoadjuvant chemotherapy (capecitabine/oxaliplatin) and chemoradiation (CRT) with or without cetuximab followed by total mesorectal excision (TME) in patients with MRI-defined high-risk rectal cancer. ASCO 2011 Gastrointestinal Cancers Symposium. J Clin Oncol 2011;29:(suppl 4; abstr 360).
- Dicle O, Obuz F, Cakmakci H. Differentiation of recurrent rectal cancer and scarring with dynamic MR imaging. Br J Radiol 1999;72:1155–1159.
- Di Fabio F, Pinto C, Fanti S, et al. Correlation between FDG-PET and pathologic response in patients with rectal cancer treated with neoadjuvant chemo-radiotherapy: First results of the Bologna Project. Proc Am Soc Clin Oncol 2005;23:(abstr 3623).
- DiPetrillo TA, Pricolo V, Sikov WM, et al. Neoadjuvant bevacizumab, oxaliplatin, 5-fluorouracil and radiation in clinical stage II–III rectal cancer. J Clin Oncol 2008;26:15S.
- Dixon AR, Thornton-Holmes J, Cheetham NM. General paractitioner´s awareness of colorectal cancer; A 10 year review. BMJ 1990;301:152-153.
- Dodds S, Dodds A, Vakis S, et al. The value of various factors associated with rectal bleeding in the diagnosis of rectal cancer. Gut 1999;44:A99.
- Dresen RC, Beets GL, Rutten HJ, et al. Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy. Part I. Are we able to predict tumor confined to the rectal wall? Radiology 2009;252:71–80.
- Dresen RC, Kusters M, Daniels-Gooszen AW, et al. Absence of tumor invasion into pelvic structures in locally recurrent rectal cancer: prediction with preoperative MR imaging. Radiology 2010;256:143–150.
- Du CZ, Xue WC, Cai Y, Li M, Gu J. Lymphovascular invasion in rectal cancer following neoadjuvant radiotherapy: a retrospective cohort study. World J Gastroenterol 2009;15:3793–3798.
- Dugdale PE, Miles KA, Bunce I, Kelley BB, Leggett DA. CT measurement of perfusion and permeability within lymphoma masses and its ability to assess grade, activity, and chemotherapeutic response. J Comput Assist Tomogr 1999;23(4):540–547.
- Dukes CD. The classification of cancer of the rectum. J Pathol Bacteriol 1932;35:323-332.
- Dworak O. Number and size of lymph nodes and node metastases in rectal carcinomas. Surg Endosc 1989;3:96–99.
- Dworak O. Morphology of lymph nodes in the resected rectum of patients with rectal carcinoma. Pathol Res Pract 1991;187:1020–1024
- Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 1997;12:19–23.

- Dzik-Jurasz A, Domenig C, George M, et al. Diffusion MRI for prediction of response of rectal cancer to chemoradiation. Lancet 2002;360:307-308.

- Eddy HA. Alterations in tumor microvasculature during hyperthermia. Radiology 1980;137:515–521.
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds) AJCC cancer staging manual, 7th edition. Springer; New York, 2010.
- Eguchi S, Kohara N, Komuta K, Kanematsu T. Mutations of the p53 gene in the stool of patients with resectable colorectal cancer. Cancer 1996;77(8 Suppl):1707-1710.
- Ellis BG, Baig KM, Senapati A, et al. Common modes of presentation of colorectal cancer patients. Colorect Dis 1999;1:Suppl 2,4.
- Enck P, Heyer T, Gantke B, et al. How reproducible are measures of the anal sphincter muscle diameter by endoanal ultrasound? Am J Gastroenterol 1997;92:293–296.
- Engenhart R, Kimmig BN, Strauss LG, et al: Therapy monitoring of presacral recurrences after high-dose irradiation: Value of PET, CT, CEA and pain score. Strahlenther Onkol 1992;168:203-212.
- Evans J, Patel U, Brown G. Rectal Cancer: Primary Staging and Assessment After Chemoradiotherapy. Semin Radiat Oncol 2011;21:169-177.
- Even-Sapir E, Parag Y, Lerman H, et al. Detection of recurrence in patients with rectal cancer: PET/CT after abdominoperineal or anterior resection. Radiology 2004;232:815–822.
- Evers K, Laufer I Gordon RL et al. Double contrast enema examination for detection of rectal carcinoma. Radiology 1981;140:635–639.

- Fernández-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
- Figueiras RG, Goh V, Padhani AR, Naveira AB, Caamaño AG, Martin CV. The role of functional imaging in colorectal cancer. AJR Am J Roentgenol 2010;195(1):54-66.
- Figueredo A, Zuraw L, Wong RK, et al. Cancer Care Ontario's Program in Evidence-based Care's Gastrointestinal Cancer Disease Site Group. The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer: A practice guideline. BMC Med 2003;1:1.
- Filippone A, Ambrosini R, Fuschi M, et al: Preoperative T and N staging of colorectal cancer: accuracy of contrast-enhanced multi-detector row CT colonography – initial experience. Radiology 2004;231:83–90.
- Finan PJ, Ritchie JK, Hawley PR. Synchronous and "early" metachronous carcinomas of the colon and rectum. Br J Surg 1987;74:945-947.
- Fisher B, Wolmark N, Rockette H, et al: Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: Results from NSABP protocol R-01. J Natl Cancer Inst 1988;80:21-29.
- Fisher SE, Daniels IR. The clinical presentation of colorectal cancer. In Brown G (ed.) Colorectal Cancer. Cambridge University Press; Cambridge, 2007.
- Flamen P, Stroobants S, Van Cutsem E, et al. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. J Clin Oncol 1999;17:894–901.
- Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994;331(25):1669-1674.
- Fukunaga H, Sekimoto M, Ikeda M et al. Fusion image of positron emission tomography and computed tomography for the diagnosis of local recurrence of rectal cancer. Ann Surg Oncol 2004;12:1–9.

- Gagliardi G, Bayar S, Smith R, Salem RR. Preoperative staging of rectal cancer using magnetic resonance imaging with external phase-arrayed coils. Arch Surg 2002;137:447–451.
- Garcia-Aguilar J, Pollack J, Lee SH, et al. Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. Dis Colon Rectum 2002;45:10–15.
- Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, et al. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. Dis Colon Rectum 2003;46:298–304.

- Garvican L. Planning for a possible national colorectal cancer screening programme. J Med Screen 1998;5:187-194.
- Gavioli M, Bagni A, Piccagli I, et al. Usefulness of endorectal ultrasound after pre-operative radiotherapy in rectal cancer. Comparison between sonographic and histopathologic changes. Dis Colon Rectum 2000;43:1075-1083.
- Genna M, Leopardi F, Valloncini E, Veraldi GF. Results of preoperative staging using endosonography in rectal cancer. Minerva Chir 2000;55:409–414.
- George ML, Dzik-Jurasz AS, Padhani AR, et al. Non-invasive methods of assessing angiogenesis and their value in predicting response to treatment in colorectal cancer. Br J Surg 2001;88:1628–1636.
- Gérard JP, Conroy T, Bonnetain F, et al.: Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. J Clin Oncol 2006;24:4620–4625.
- Giordano P, Efron J, Vernava AM et al. Strategies of follow-up for colorectal cancer: a survey of the American Society of Colon and Rectal Surgeons. Tech Coloproctol 2006;10:199–207.
- Giovannucci E. Epidemiologic studies of folate and colorectal neoplasia: a review. J Nutr 2002; 132:2350S-2355S.
- Glaser F, Schlag P, Herfarth C. Endorectal ultrasonography for the assessment of invasion of rectal tumors and lymph node involvement. Br J Surg 1990;77:883–887.
- Glimelius B, Påhlman L, Cervantes A, ESMO Guidelines Working Group. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(Suppl 5):v82–86.
- Goh V, Halligan S, Hugill JA, Gartner L, Bartram CI. Quantitative colorectal cancer perfusion measurement using dynamic contrast-enhanced multidetector-row computed tomography: effect of acquisition time and implications for protocols. J Comput Assist Tomogr 2005a;29(1):59–63.
- Goh V, Halligan S, Hugill JA et al. Quantitative colorectal cancer perfusion measurements using MDCT: inter and intra-observer agreement. AJR Am J Roentogenol 2005b;185:225–231.
- Goh V, Halligan S, Gharpuray A, Wellsted D, Sundin J, Bartram CI. Quantitative Assessment of Colorectal Cancer Tumor Vascular Parameters by Using Perfusion CT: Influence of Tumor Region of Interest. Radiology 2007;247:726-732.
- Goh V, Halligan S, Gharpuray A, Wellsted D, Sundin J, Bartram CI. Quantitative Assessment of Colorectal Cancer Tumor Vascular Parameters by Using Perfusion CT: Influence of Tumor Region of Interest. Radiology 2008a; 247:726-732.
- Goh V, Halligan S, Daley F, Wellsted DM, Guenther T, Bartram CI. Colorectal tumor vascularity: quantitative assessment with multidetector CT - do tumor perfusion measurements reflect angiogenesis? Radiology 2008b;249(2):510-517.
- Goh V, Halligan S, Wellsted DM, Bartram CI. Can perfusion CT assessment of primary colorectal adenocarcinoma blood flow at staging predict for subsequent metastatic disease? A pilot study. Eur Radiol 2009a;19:79–89.
- Goh V, Bartram C, Halligan S. Effect of intravenous contrast agent volume on colorectal cancer vascular parameters as measured by perfusion computed tomography. Clin Radiol 2009b;64:368-372.
- Gold DM, Halligan S, Kmiot WA, Bartram CI. Intraobserver and interobserver agreement in anal endosonography. Br J Surg 1999;86:371–375.
- Goldberg RM, Fleming TR, Tangen CM et al. Surgery for recurrent colon cancer: strategies for identifying resectable recurrence and success rates after resection. Eastern cooperative oncology group, the North central cancer treatment group, and the Southwest oncology group. Ann Intern Med 1998;129:27–35.
- Goldman S, Arvidsson H, Norming U, Lagerstedt U, Magnusson I, Frisell J. Transrectal ultrasound and computed tomography in preoperative staging of lower rectal adenocarcinoma. Gastrointest Radiol 1991;16:259–263.
- Goldstein NS, Turner JR, Pericolonic tumor deposits in patients with T3N+MO colon adenocarcinomas: markers of reduced disease free survival and intra-abdominal metastases and their implications for TNM classification. Cancer 2000;88(10):2228–2238.
- Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. Am J Prev Med 2007;32(3):210-216.
- Gosens MJ, Van Krieken JH, Marijnen CA et al. Improvement of staging by combining tumor and treatment parameters: the value of prognostication in rectal cancer. Clin Gastroenterol Hepatol 2007;5:997–1003.
- Govindarajan A, Coburn NG, Kiss A, Rabeneck L, Smith AJ, Law CH. Population-based assessment of the surgical management of locally advanced colorectal cancer. J Natl Cancer Inst 2006;98:1474–1481.

- Grabbe E, Lierse W, Winkler R. The perirectal fascia: morphology and use in staging of rectal carcinoma. Radiology 1983;149:241–246.
- Grann A, Minsky BD, Cohen AM et al. Preliminary results of preoperative 5-fluorouracil, low-dose leucovorin, and concurrent radiation therapy for clinically resectable T3 rectal cancer. Dis Colon Rectum 1997;40:512–522.
- Grassetto G, Marzola MC, Minicozzi A, Al-Nahhas A, Rubello D. F-18 FDG PET/CT in rectal carcinoma: where are we now? Clin Nucl Med 2011;36(10):884-888.
- Greene FL, Compton CC, Fritz AG, Shah GP, Winchester DP (eds) AJCC Cancer Staging Atlas. Springer; New York, 2006.
- Gu J, Khong PL, Wang S, Chan Q, Law W, Zhang J. Quantitative assessment of diffusion-weighted MR imaging in patients with primary rectal cancer: correlation with FDG-PET/CT. Mol Imaging Biol 2011;13:1020–1028.
- Gualdi GF, Casciani E, Guadalaxara A, d'Orta C, Polettini E, Pappalardo G. Local staging of rectal cancer with transrectal ultrasound and endorectal magnetic resonance imaging: comparison with histologic findings. Dis Colon Rectum 2000;43:338–345.
- Guillem JG, Forde KA, Treat MR, Neugut AI, O'Toole KM, Diamond BE. Colonoscopic screening for neoplasms in asymptomatic first-degree relatives of colon cancer patients. A controlled, prospective study. Dis Colon Rectum 1992;35(6):523-529.
- Guillem JG, Chessin DB, Cohen AM et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005;241:829–838.
- Guimaraes R, Clement O, Bittoun J, Carnot F, Frija G. MR lymphography with superparamagnetic iron nanoparticles in rats: pathologic basis for contrast enhancement. AJR Am J Roentgenol 1994;162:201-207.
- Guinet C, Buy JN, Ghossain MA, et al. Comparison of magnetic resonance imaging and computed tomography in the preoperative staging of rectal cancer. Arch Surg 1990;125:385–388.
- Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: A pooled analysis. J Clin Oncol 2004;22:1785-1796.
- Gunther K, Dworak O, Remke S, Pfluger R, Merkel S, Hohenberger W, et al. Prediction of distant metastases after curative surgery for rectal cancer. J Surg Res 2002;103:68-78.

- Haberkorn U, Strauss LG, Dimitrakopoulou A, et al: PET studies of fluorodeoxyglucose metabolism in patients with recurrent colorectal tumors receiving radiotherapy. J Nucl Med 1991;32:1485-1490.
- Habr-Gama A, de Souza PM, Ribeiro U et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum 1998;41:1087–1096.
- Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg. 2006;10:1319–1328.
- Habr-Gama A, Perez RO, Proscurshim I, et al. Absence of lymph nodes in the resected specimen after radical surgery for distal rectal cancer and neoadjuvant chemoradiation therapy: what does it mean? Dis Colon Rectum 2008;51:277–283.
- Hadfield MB, Nicholson AA, MacDonald AW, et al. Preoperative staging of rectal carcinoma by magnetic resonance imaging with a pelvic phased-array coil. Br J Surg 1997;84:529–531.
- Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 2005;237(3):893-904.
- Halligan S, Altman D, Mallett S, et al. CT colonography: multi-reader multi-case (MRMC) assessment of performance with and without computer assisted detection. Gastroenterology 2006;131:1690-1699.
- Halligan S. Screening for colorectal cancer. In Brown G (ed.) Colorectal Cancer. Cambridge University Press; Cambridge, 2007.
- Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332(13):839-847.
- Harisinghani MG, Barentsz JO, Hahn PF, et al. MR lymphangiography for detection of minimal nodal disease in patients with prostate cancer. Acad Radiol 2002;9(suppl 2):S312–S313.
- Harrison JC, Dean PJ, el-Zeky F et al. From Dukes through Jass: pathological prognostic indicators in rectal cancer. Hum Pathol 1994;25:498–505.

- Hartman TJ, Tangrea JA, Pietinen P, et al. Tea and coffee consumption and risk of colon and rectal cancer in middle-aged Finnish men. Nutr Cancer 1998;31(1):41-48.
- Harvey C, Dooher A, Morgan J, Blomley M, Dawson P. Imaging of tumour therapy responses by dynamic CT. Eur J Radiol 1999;30(3):221–226.
- Havenga K, Enker WE, Norstein J, et al: Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: An international analysis of 1411 patients. Eur J Surg Oncol 1999;25:368-374.
- Hawkes EA, Cunningham D, Tait D, et al. Neoadjuvant Chemotherapy Alone for Early-Stage Rectal Cancer: An Evolving Paradigm? Semin Radiat Oncol 2011;21:196-202.
- Hayes RB, Sigurdson A, Moore L, et al; for the PLCO Trial Team. Methods for etiologic and early marker investigations in the PLCO trial. Mutat Res 2005;592(1-2):147-154.
- Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery-the clue to pelvic recurrence? Br J Surg1982;69(10):613-616.
- Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:1479–1482.
- Heald RJ. The 'Holy Plane' of rectal surgery. J R Soc Med 1988;81(9):503-508.
- Heald RJ, Moran BJ, Ryall RD, et al: Rectal cancer: The Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 1998;133:894-899.
- Hein PA, Kremser C, Judmaier W, et al. Diffusion-weighted magnetic resonance imaging for monitoring diffusion changes in rectal carcinoma during combined, preoperative chemoradiation: preliminary results of a prospective study. Eur J Radiol 2003;45:214-222.
- Henderson MM. International differences in diet and cancer incidence. J Natl Cancer Inst Monogr 1992;12:59-63.
- Heo S, Jeong S, Young J et al. A comparative study of histopathologic parameters and apparent diffusion coefficient values on 3T rectal MRI in locally advanced rectal cancer following neoadjuvant chemoradiation therapy (abstr). In: European Congress of Radiology (ECR) Annual Meeting Program 2010. Vienna, Austria
- Herborn CU, Lauenstein TC, Vogt FM, et al. Interstitial MR lymphography with MS-325: characterization of normal and tumor-invaded lymph nodes in a rabbit model. AJR Am J Roentgenol 2002;179:1567–1572.
- Hermanek P, Gospodarowicz MK, Hutter RVP, Sobin LH (eds) Prognostic factors in cancer. Springer; Berlin,1995.
- Herzog U, von Flue M, Tondelli P, Schuppisser JP. How accurate is endorectal ultrasound in the preoperative staging of rectal cancer? Dis Colon Rectum 1993;36:127–134.
- Hida J, Yasutomi M, Maruyama T et al. Lymph node metastases detected in the mesorectum distal to carcinoma of the rectum by the clearing method: justification of total mesorectal excision. J Am Coll Surg 1997a;184:584–588.
- Hida J, Yasutomi M, Fujimoto K et al. Does lateral lymph node dissection improve survival in rectal cancer? Examination of node metastases by the clearing method. J Am Coll Surg 1997b;184:475–480.
- Hildebrandt U, Klein T, Feifel G, Schwarz HP, Koch B, Schmitt RM. Endosonography of pararectal lymph nodes. In vitro and in vivo evaluation. Dis Colon Rectum 1990;33:863–868.
- Hildebrandt U, Feifel G. Importance of endoscopic ultrasonography staging for treatment of rectal cancer. Gastrointest Endosc Clin N Am 1995;5:843–849.
- Hiotis SP, Weber SM, Cohen AM et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 448 patients. J Am Coll Surg 2002;194:131–135.
- Ho ML, Liu J, Narra V. Magnetic Resonance Imaging of Rectal Cancer. Clin Colon Rectal Surg 2008:21:178–187.
- Hocht S, Wiegel T, Hammad R et al. Pelvic sites of recurrence in rectal cancer. Lancet 2002;360:879–880.
- Hocht S, Mann B, Germer CT et al. Pelvic sidewall involvement in recurrent rectal cancer. Int J Colorectal Dis 2004;19:108–113.
- Hodgman CG, MacCarty RL, Wolff BG, et al. Preoperative staging of rectal carcinoma by computed tomography and 0.15T magnetic resonance imaging: preliminary report. Dis Colon Rectum 1986;29:446–450.
- Hoffmann KT, Rau B, Wust P, et al. Restaging of locally advanced carcinoma of the rectum with MR imaging after preoperative radio-chemotherapy plus regional hyperthermia. Strahlenther Onkol 2002;178:386–392.
- Hojo K, Koyama Y, Moriya A et al. Lymphatic spread and its prognostic value in patients with rectal cancer. Am J Surg 1982;144:350–354.

- Horn A, Dahl O, Morild I. Venous and neural invasion as predictors of recurrence in rectal adenocarcinoma. Dis Colon Rectum 1991;34:798-804.
- Horton KM, Abrams RA, Fishman EK. Spiral CT of colon cancer: imaging features and role in management. RadioGraphics 2000;20:419–430.
- Hosonuma T, Tozaki M, Ichiba N, et al. Clinical usefulness of diffusion-weighted imaging using low and high b-values to detect rectal cancer. Magn Reson Med Sci 2006;5(4):173–177.
- Hughes R, Glynne-Jones R, Grainger J, et al. Can pathological complete response in the primary tumour following pre-operative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for sterilisation of pelvic lymph nodes, a low risk of local recurrence and the appropriateness of local excision? Int J Colorectal Dis 2006;21:11–17.
- Huguier M, Houry S, Barrier A. Local recurrence of cancer of the rectum. Am J Surg 2001;182:437–439.
- Huh JW, Park YA, Jung EJ, Lee KY, Sohn SK. Accuracy of endorectal ultrasonography and computed tomography for restaging rectal cancer after preoperative chemoradiation. J Am Coll Surg 2008;207(1):7–12.
- Huh JW, Oh BR, Kim HR, Kim YJ. Preoperative carcinoembryonic antigen level as an independent prognostic factor in potentially curative colon cancer. J Surg Oncol 2010;101:396–400.
- Hulsmans FJ, Tio TL, Fockens P, Bosma A, Tytgat GN. Assessment of tumor infiltration depth in rectal cancer with transrectal sonography: caution is necessary. Radiology 1994;190:715–720.
- Hunerbein M, Pegios W, Rau B, Vogl TJ, Felix R, Schlag PM. Prospective comparison of endorectal ultrasound, three-dimensional endorectal ultrasound, and endorectal MRI in the preoperative evaluation of rectal tumors: preliminary results. Surg Endosc 2000;14:1005–1009.
- Hunerbein M. Endorectal ultrasound in rectal cancer: Colorectal Dis 2003;5:402–405.
- Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-2342.

- Ichikawa T, Erturk SM, Motosugi U, et al. High b-value diffusion weighted MRI in colorectal cancer. AJR Am J Roentgenol 2006;187:181–184.
- Indinnimeo M, Grasso RF, Cicchini C, et al. Endorectal magnetic resonance imaging in the preoperative staging of rectal tumors. Int Surg 1996;81:419–422.

- Jager GJ, Barentsz JO, Oosterhof GO, Witjes JA, Ruijs SJ. Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR imaging with a three-dimensional TI-weighted magnetization-prepared-rapid gradient-echo sequence. AJR Am J Roentgenol 1996; 167:1503–1507.
- Jain R, Scarpace LM, Ellika S, et al. Imaging response criteria for recurrent gliomas treated with bevacizumab: role of diffusion weighted imaging as an imaging biomarker. J Neurooncol 2010;96:423–431.
- Janjan NA, Abbruzzese J, Pazdur R, et al. Prognostic implications of response to preoperative infusional chemoradiation in locally advanced rectal cancer. Radiother Oncol 1999;51:153–160.
- Janjan NA, Crane C, Feig BW, et al. Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 2001;24:107–112.
- Jass JR, Love SB. Prognostic value of direct spread in Dukes' C cases of rectal cancer. Dis Colon Rectum 1989;32:477–480.
- Janssen MH, Ollers MC, Riedl RG, et al. Accurate prediction of pathological rectal tumor response after two weeks of preoperative radiochemotherapy using (18)F-fluorodeoxyglucose-positron emission tomography-computed tomography imaging. Int J Radiat Oncol Biol Phys. 2010;77:392–329.
- Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57(1):43-66.
- Jessup JM, Menk HR, Fremgen A et al. Diagnosing colorectal carcinoma: clinical and molecular approaches. CA Cancer J Clin 1997;47:70–92.
- Johnson JA, Wilson TA. A model for capillary exchange. Am J Physiol 1966;210(6):1299–1303.
- Jonas J, Bahr R. Neoadjuvant chemoradiation treatment impairs accuracy of MRI staging in rectal carcinoma. Gut 2006;55:1214–1215.
- Jonker DJ, O'Callaghan CJ, Karapetis CS, et al: Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-2048.
- Julien LA, Thorson AG. Current Neoadjuvant Strategies in Rectal Cancer. J Surg Oncol 2010;101:321–326.

- Kahn H, Alexander A, Rakinic J, et al: Preoperative staging of irradiated rectal cancers using digital rectal examination, computed tomography, endorectal ultrasound, and magnetic resonance imaging does not accurately predict T0, N0 pathology. Dis Colon Rectum 1997;40:140–144.
- Kambadakone AV, Sahani DV. Body Perfusion CT: Technique, Clinical Applications, and Advances. Radiol Clin N Am 2009;47:161–178.
- Kamel IR, Cohade C, Neyman E et al. Incremental value of CT in PET/CT of patients with colorectal carcinoma. Abdom Imaging 2004;29:663–668.
- Kaminsky-Forrett MC, Conroy T, Luporsi E et al. Prognostic implications of downstaging following preoperative radiation therapy for operable T3–T4 rectal cancer. Int J Radiat Oncol Biol Phys 1998;42:935–941.
- Kan Z, Phongkitkarun S, Kobayashi S, et al. Functional CT for Quantifying Tumor Perfusion in Antiangiogenic Therapy in a Rat Model. Radiology 2005;237:151–158.
- Kang JH, Kim YC, Kim H, et al. Tumor volume changes assessed by three-dimensional magnetic resonance volumetry in rectal cancer patients after preoperative chemoradiation: the impact of the volume reduction ratio on the prediction of pathologic complete response. Int J Radiat Oncol Biol Phys 2010;76(4):1018–1025.
- Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl JMed 2001;345:638–646.
- Katsura Y, Yamada K, Ishizawa T, Yoshinaka H, Shimazu H. Endorectal ultrasonography for the assessment of wall invasion and lymph node metastasis in rectal cancer. Dis Colon Rectum 1992;35:362–368.
- Kelvin FM, Gardiner R, Vas W et al. Colorectal carcinomas missed on double contrast barium enema study: a problem perception. AJR Am J Roentgenol 1981;137:307.
- Kerber RA, Slattery ML, Potter JD, Caan BJ, Edwards SL. Risk of colon cancer associated with a family history of cancer or colorectal polyps: the diet, activity, and reproduction in colon cancer study. Int J Cancer 1998;78(2):157-160.
- Kikendall JW, Bowen PE, Burgess MB, Magnetti C, Woodward J, Langenberg P. Cigarettes and alcohol as independent risk factors for colonic adenomas. Gastroenterology 1989;97(3):660-664.
- Kim JH, Beets GL, Kim MJ, Kessels AG, Beets-Tan RG. High-resolution MRI for nodal staging in rectal cancer: Are there any criteria in addition to the size? Eur J Radiol 2004;52:78–83.
- Kim NK, Kim MJ, Yun SH, Sohn SK, Min JS. Comparative study of transrectal ultrasonography, pelvic computerized tomography, and magnetic resonance imaging in preoperative staging of rectal cancer. Dis Colon Rectum 1999;42:770–775.
- Kim NK, Kim MJ, Park JK, Park SI, Min JS. Preoperative staging of rectal cancer with MRI: accuracy and clinical usefulness. Ann Surg Oncol 2000;7(10):732–737.
- Kim SH, Lee JM, Hong SH, et al. Locally advanced rectal cancer: added value of diffusion-weighted MR imaging in the evaluation of tumor response to neoadjuvant chemo- and radiation therapy. Radiology 2009;253:116–125.
- Kim SH, Lee JY, Lee JM, Han JK, Choi BI. Apparent diffusion coefficient for evaluating tumour response to neoadjuvant chemoradiation therapy for locally advanced rectal cancer Eur Radiol 2011:21:987-995.
- Kim YC, Lim JS, Keum KC et al. Comparison of diffusion-weighted MRI and MR volumetry in the evaluation of early treatment outcomes after preoperative chemoradiotherapy for locally advanced rectal cancer. J Magn Reson Imaging. 2011 Jul 12. DOI: 10.1002/jmri.22696. [Epub ahead of print].
- Kim YH, Kim DY, Kim TH, et al. Usefulness of magnetic resonance volumetric evaluation in predicting response to preoperative concurrent chemoradiotherapy in patients with resectable rectal cancer. Int J Radiat Oncol Biol Phys 2005;62(3):761–768.
- Kinkel K, Tardivon AA, Soyer P, et al. Dynamic contrast-enhanced subtraction versus T2-weighted spin-echo MR imaging in the follow-up of colorectal neoplasm: a prospective study of 41 patients. Radiology 1996;200:453–458.
- Köckerling F, Reymond MA, Altendorf-Hofmann A, et al. Influence of surgery on metachronous distant metastases and survival in rectal cancer. J Clin Oncol 1998;16:324–329.
- Koh DM, Brown G, Temple L, et al. Rectal cancer: mesorectal lymph nodes at MR imaging with USPIO versus histopathologic findings—initial observations. Radiology 2004;231:91–99.
- Koh DM, Brown G, Temple L et al. Distribution of mesorectal lymph nodes in rectal cancer: in vivo MR imaging compared with histopathological examiantion. Initial observations. Eur Radiol 2005;15:1650–1657.
- Koh DM, Brown G, Husband JE. Nodal staging in rectal cancer. Abdom Imaging 2006;31:652–659.

- Koh DM, Padhani AR. Diffusion-weighted MRI: a new functional clinical technique for tumor imaging. Br J Radiol 2006:79:633–635.
- Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol 2007;188:1622–1635.
- Koh DM, Scurr E, Collins D, et al. Predicting response of colorectal hepatic metastasis: value of pretreatment apparent diffusion coefficients.AJR Am J Roentgenol 2007;188:1001–1008.
- Koh DM, Chau I, Tait D, et al. Evaluating mesorectal lymph nodes in rectal cancer before and after chemoradiation using thin-section T2-weighted magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2008;71:456–461.
- Koh DM, George C, Temple L et al. Diagnostic Accuracy of Nodal Enhancement Pattern of Rectal Cancer at MRI Enhanced With Ultrasmall Superparamagnetic Iron Oxide: Findings in Pathologically Matched Mesorectal Lymph Nodes AJR Am J Roentgenol 2010;194:W505–W513.
- Kraemer M, Wiratkapun S, Seow-Choen F et al. Stratifying risk factors for follow-up: a comparison of recurrent and nonrecurrent colorectal cancer. Dis Colon Rectum 2001;44:815–821.
- Krasna MJ, Flancbaum L, Cody RP, Shneibaum S, Ben Ari G. Vascular and neural invasion in colorectal carcinoma. Incidence and prognostic significance. Cancer 1988;61:1018-23.
- Kremser C, Judmaier W, Hein P, Griebel J, Lukas P, DeVries A. Preliminary Results on the Influence of Chemoradiation on Apparent Diffusion Coefficients of Primary Rectal Carcinoma Measured by Magnetic Resonance Imaging. Strahlenther Onkol 2003;179:641–649.
- Kristiansen C, Loft A, Berthelsen AK, et al. PET/CT and histopathologic response to preoperative chemoradiation therapy in locally advanced rectal cancer. Dis Colon Rectum 2008;51:21–25.
- Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-715.
- Kuo LJ, Chern MC, Tsou MH, et al. Interpretation of magnetic resonance imaging for locally advanced rectal carcinoma after preoperative chemoradiation therapy. Dis Colon Rectum 2005;48(1):23–28.
- Kusunoki M, Yanagi H, Kamikonya N, et al. Preoperative detection of local extension of carcinoma of the rectum using magnetic resonance imaging. J Am Coll Surg 1994;179(6):653–656.
- Kuvshinoff B, Maghfoor I, Miedema B, et al. Distal margin requirements after preoperative chemoradiotherapy for distal rectal carcinomas: are < or = 1 cm distal margins sufficient? Ann Surg Oncol 2001;8(2):163-169.
- Kwok H, Bissett IP, Hill GL. Preoperative staging of rectal cancer. Int J Colorectal Dis 2000;15:9–20.

- Lahaye MJ, Engelen SM, Nelemans PJ et al. Imaging for predicting the risk factors-the circumferential resection margin and nodal disease-of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR 2005;26(4):259-268.
- Lahaye MJ, Engelen SM, Kessels AG, et al. USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer: predictive criteria. Radiology 2008;246:804–811.
- Lahaye MJ, Beets GL, Engelen SME, et al. Gadovosfeset Trisodium (Vasovist ®) enhanced MR lymph node detection: initial observations. Open Magnetic Reson J 2009a;2:1–5.
- Lahaye MJ, BeetsGL, Engelen SME, et al. Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy. Part II. What are the criteria to predict involved lymph nodes? Radiology 2009b;252:71–80.
- Lambrecht M, Deroose C, Roels S et al. The use of FDG-PET/CT and diffusion-weighted magnetic resonance imaging for response prediction before, during and after preoperative chemoradiotherapy for rectal cancer. Acta Oncol 2010:49:956–963.
- Lambregts DM, Beets GL, Maas M, et al. Accuracy of Gadofosveset-enhanced MRI for Nodal Staging and Restaging in Rectal Cancer. Ann Surg 2011a;253:539–545.
- Lambregts DM, Maas M, Riedl RG, et al. Value of ADC measurements for nodal staging after chemoradiation in locally advanced rectal cancer-a per lesion validation study. Eur Radiol 2011b;21(2):265-273.
- Lambregts DM, Vandecaveye V, Barbaro B, et al. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. Ann Surg Oncol 2011c;18(8):2224-2231.
- Lambregts DM, Cappendijk VC, Maas M, Beets GL, Beets-Tan RG. Value of MRI and diffusion-weighted MRI for the diagnosis of locally recurrent rectal cancer. Eur Radiol 2011d;21(6):1250-1258.
- Larsson SC, Giovannucci E, Wolk A. Vitamin B_6 intake, alcohol consumption, and colorectal cancer: a longitudinal population-based cohort of women. Gastroenterology 2005;128:1830-1837.

- Lee A, Weissleder R, Brady T, Wittenberg J. Lymph nodes: microstructural anatomy at MR imaging. Radiology 1991;178:519-522.
- Lee P, Oyama K, Homer L, Sullivan E. Effects of endorectal ultrasonography in the surgical management of rectal adenomas and carcinomas. Am J Surg 1999;177:388–391.
- Lee TY, Purdie TG, Stewart E. CT imaging of angiogenesis. Q J Nucl Med 2003;47:171–187.
- Leek RD, Landers RJ, Harris AL, et al. Necrosis correlates with high vascular density and focal macrophage infiltration in invasive carcinoma of the breast. Br J Cancer 1999;79:991–995.
- Lehnert T, Methner M, Pollok A, Schaible A, Hinz U, Herfarth C. Multivisceral resection for locally advanced primary colon and rectal cancer: an analysis of prognostic factors in 201 patients. Ann Surg 2002;235:217–225.
- Leite JS, Martins SC, Oliveira J, Cunha MF, Castro-Sousa F. Clinical significance of macroscopic completeness of mesorectal resection in rectal cancer. Colorectal Dis 2011;13(4):381-386.
- Levin B, Brooks D, Smith RA, Stone A. Emerging technologies in screening for colorectal cancer: CT colonography, immunochemical fecal occult blood tests, and stool screening using molecular markers. CA Cancer J Clin 2003;53:44-55.
- Lezoche E, Guerrieri M, Paganini AM, Baldarelli M, De Sanctis A, Lezoche G. Long-term results in patients with T2–3 N0 distal rectal cancer undergoing radiotherapy before transanal endoscopic microsurgery. Br J Surg 2005;92:1546–1552.
- Lezoche G, Baldarelli M, Guerrieri M, et al. A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy. Surg Endosc 2008;22:352–358.
- Lim HK, Kim JK, Kim KA, Cho KS. Prostate cancer: apparent diffusion coefficient map with T2-weighted images for detection—a multireader study. Radiology 2009;250:145–151.
- Llamas-Elvira JM, Rodriguez-Fernandez A, Gutierrez-Sainz J, et al. Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. Eur J Nucl Med Mol Imaging 2007;34:859–867.
- Longo WE, Johnson FE. The preoperative assessment and postoperative surveillance of patients with colon and rectal cancer. Surg Clin North Am 2002;82:1091–1108.
- Losi L, Luppi G, Gavioli M, et al. Prognostic value of Dworak grade of regression (GR) in patients with rectal carcinoma treated with preoperative radiochemotherapy. Int J Colorectal Dis 2006;21:645–651.
- Luna-Perez P, Bustos-Cholico E, Alvarado I et al. Prognostic significance of circumferential margin involvement in rectal adenocarcinoma treated with preoperative chemradiotherapy and low anterior resection. J Surg Oncol 2005;90:20–25.

- Maas M, Nelemans P, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835–844.
- Machiels JP, Sempoux C, Scalliet P, et al: Phase I/II study of preoperative cetuximab, capecitabine, and external beam radiotherapy in patients with rectal cancer. Ann Oncol 2007;18:738-744.
- Mack MG, Balzer JO, Straub R, Eichler K, Vogl TJ. Superparamagnetic iron oxide-enhanced MR imaging of head and neck lymph nodes. Radiology 2002;222:239-244.
- Maier AG, Kersting-Sommerhoff B, Reeders JW, et al. Staging of rectal cancer by double-contrast MR imaging using the rectally administered superparamagnetic iron oxide contrast agent ferristene and IV gadodiamide injection: results of a multicenter phase II trial. J Magn Reson Imaging 2000;12(5):651–660.
- Maldjian C, Smith R, Kilger A, Schnall M, Ginsberg G, Kochman M. Endorectal surface coil MR imaging as a staging technique for rectal carcinoma: a comparison study to rectal endosonography. Abdom Imaging 2000;25:75–80.
- Mancini R, Cosimelli M, Filippini A, et al. Nerve-sparing surgery in rectal cancer: feasibility and functional results. J Exp Clin Cancer Res 2000;19(1):35-40.
- Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: clinicopathologic correlations. Cancer 1994;73(11):2680–2686.
- Mang T, Maier A, Plank C, Mueller-Mang C, Herold C, Schima W. Pitfalls in Multi–Detector Row CT Colonography: A Systematic Approach. RadioGraphics 2007;27:431–454.
- Maretto I, Pomerri F, Pucciarelli S, et al. The potential of restaging in the prediction of pathologic response after preoperative chemoradiotherapy for rectal cancer. Ann Surg Oncol 2007;14:455–461.
- Marijnen CA, Glimelius B. The role of radiotherapy in rectal cancer. Eur J Cancer 2002;38:943–952.

- Marijnen CA, van de Velde CJ, Putter H, et al: Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomized trial. J Clin Oncol 2005;23:1847-1858.
- Markus J, Morrissey B, deGara C et al. MRI of recurrent rectosigmoid carcinoma. Abdom Imaging 1997;22:338–342.
- Marone P, Petrulio F, de Bellis M, Battista Rossi G, Tempesta A. Role of endoscopic ultrasonography in the staging of rectal cancer: a retrospective study of 63 patients. J Clin Gastroenterol 2000;30:420–424.
- Marra G, Boland CR. DNA repair and colorectal cancer. Gastroenterol Clin North Am 1996;25(4):755-772.
- Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet 2000;356:93–96.
- Massari M, De Simone M, Cioffi U, Rosso L, Chiarelli M, Gabrielli F. Value and limits of endorectal ultrasonography for preoperative staging of rectal carcinoma. Surg Laparosc Endosc 1998;8:438–444.
- Mathur P, Smith JJ, Ramsey C et al. Comparison of CT and MRI in the pre-operative staging of rectal adenocarcinoma and prediction of circumferential margin involvement by MRI. Colorectal Dis 2003;5:396–401.
- Matsuoka H, Nakamura A, Sugiyama M, Hachiya J, Atomi Y, Masaki T. MRI diagnosis of mesorectal lymph node metastasis in patients with rectal carcinoma. What is the optimal criterion? Anticancer Res 2004;24:4097–4101.
- McCollum AD, Kocs DM, Chada P, et al. A randomized phase II trial of preoperative chemoradiotherapy with or without cetuximab in locally advanced adenocarcinoma of the rectum. J Clin Oncol 2010;28:15S.
- McCullough ML, Robertson AS, Rodriguez C, et al. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). Cancer Causes Control 2003;14(1):1-12.
- McLachlan SJ, Morris MR, Lucas MA, et al. Phase I clinical evaluation of a new iron oxide MR contrast agent. J Magn Reson Imaging 1994;4:301-307.
- McMichael AJ, Giles GG. Cancer in migrants to Australia: extending the descriptive epidemiological data. Cancer Res 1988;48(3):751-756.
- Medich D, McGinty J, Parda D, et al. Preoperative chemoradiotherapy and radical surgery for locally advanced distal rectal adenocarcinoma. Dis Colon Rectum 2001;44:1123–1128.
- MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006;333:779.
- Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 2001;16:298–304.
- Meyenberger C, Huch Boni RA, Bertschinger P, Zala GF, Klotz HP, Krestin GP. Endoscopic ultrasound and endorectal magnetic resonance imaging: a prospective, comparative study for preoperative staging and follow-up of rectal cancer. Endoscopy 1995;27:469–479.
- Middleton PF, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. Dis Colon Rectum 2005;48:270–284.
- Miles KA, Charnsangavej C, Lee FT, Fishman EK, Horton K, Lee TY. Application of CT in the investigation of angiogenesis in oncology. Acad Radiol 2000;7(10):840–850.
- Miles KA. Perfusion CT for the assessment of tumour vascularity: which protocol? Br J Radiol 2003;76(spec no 1):S36–S42.
- Miller RE, Lehman G. Polypoid colonic lesions undetected by endoscopy. Radiology 1978;129:295-297.
- Miller AR. Multidisciplinary management of recurrent colorectal cancer. Surg Oncol 1998;7:209–221.
- Milsom JW, Graffner H. Intrarectal ultrasonography in rectal cancer staging and in the evaluation of pelvic disease: clinical uses of intrarectal ultrasound. Ann Surg 1990;212:602–606.
- Mizukami Y, Ueda S, Mizumoto A, et al. Diffusion-weighted Magnetic Resonance Imaging for Detecting Lymph Node Metastasis of Rectal Cancer. World J Surg 2011;35:895–899.
- Mohiuddin M, Hayne M, Regine WF, et al. Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. Int J Radiat Oncol Biol Phys 2000;48:1075–1080.
- Monig SP, Baldus SE, Zirbes TK, et al. Lymph node size and metastatic infiltration in colon cancer. Ann Surg Oncol 1999;6:579–581

- Moore HG, Akhurst T, Larson SM, et al. A case-controlled study of 18-fluorodeoxyglucose positron emission tomography in the detection of pelvic recurrence in previously irradiated rectal cancer patients. J Am Coll Surg 2003;197:22-28.
- Moran MR, James EC, Rothenberger DA et al. Prognostic value of positive lymph nodes in rectal cancer. Dis Colon Rectum 1992;35:579–581.
- Morgan B, Thomas AL, Drevs J, et al. Dynamic contrast enhanced magnetic resonance imaging as a biomarker for the pharmacological response of PTK787/ZK 222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases, in patients with advanced colorectal cancer and liver metastases: results from two phase I studies. J Clin Oncol 2003;21:3955–3964.
- Morikawa E, Yasutomi M, Shindou K et al. Distribution of metastatic lymph nodes in colorectal cancer by the modified clearing method. Dis Colon Rectum 1994;37:219–223.
- Morino M, Parini U, Giraudo G, Salval M, Brachet Contul R, Garrone C. Laparoscopic total mesorectal excision: a consecutive series of 100 patients. Ann Surg 2003;237(3):335-342.
- Mukherjee A. Total pelvic exenteration for advanced rectal cancer. S D J Med 1999;52(5):153-156.
- Muthusamy VR, Chang KJ. Optimal methods for staging rectal cancer. Clin Cancer Res 2007;13(22pt2):6877s–6884s.

- Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH: Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol 2002;26:350–357.
- Nagtegaal ID, Gosens M J, Marijnen CA et al. Combinations of tumor and treatment parameters are more discriminative for prognosis than the present TNM system in rectal cancer. J Clin Oncol 2007;25:1647–1650.
- Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303–312.
- Namimoto T, Awai K, Nakaura T, Yanaga Y, Hirai T, Yamashita Y. Role of diffusion-weighted imaging in the diagnosis of gynecological diseases. Eur Radiol 2009;19:745–760.
- Napoleon B, Pujol B, Berger F, et al. Accuracy of endosonography in the staging of rectal cancer treated by radiotherapy. Br J Surg 1991;78:785-788.
- Nelson H, Petrelli N, Carlin A, et al. National Cancer Institute Expert Panel. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583–596.
- Nelson RL, Persky V, Turyk M. Determination of factors responsible for the declining incidence of colorectal cancer. Dis Colon Rectum 1999;42(6):741-752.
- Nesbakken A, Nygaard K, Westerheim O, et al. Local recurrence after mesorectal excision for rectal cancer. Eur J Surg Oncol 2002;28:126-134.
- Newland R, Dent O, Lyttle M, Chapuis P, Bokey E. Pathological determinants of survival associated with colorectal cancer with lymph node metastases. Cancer 1994;73:2076-2082.
- NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444–1450.
- Nishie A, Stolpen AH, Obuchi M, Kuehn DM, Dagit A, Andresen K. Evaluation of locally recurrent pelvic malignancy: performance of T2- and diffusion-weighted MRI with image fusion. J Magn Reson Imaging 2008;28:705–713.
- Nogue M, Salud A, Vicente P, et al: Addition of bevacizumab to induction plus concominant capecitabine-oxaliplatin (XELOX) chemoradiotherapy (CRT) in MRI poor prognosis locally advanced rectal cancer: Avacross study. J Clin Oncol 2009;27:4100(abstr).

- Obrocea F, Sajin M, Marinescu EC, Stoica D. Colorectal cancer and the 7th revision of the TNM staging system: review of changes and suggestions for uniform pathologic reporting. Rom J Morphol Embryol 2011;52(2):537–544.
- Okizuka H, Sugimura K, Ishida T. Preoperative local staging of rectal carcinoma with MR imaging and a rectal balloon. J Magn Reson Imaging 1993;3:329–335.
- Okizuka H, Sugimura K, Yoshizako T, Kaji Y, Wada A. Rectal carcinoma: prospective comparison of conventional and gadopentetate dimeglumine enhanced fat-suppressed MR imaging. J Magn Reson Imaging 1996;6(3):465–471.
- Oku S, Nakagawa K, Momose T, et al. FDG-PET after radiotherapy is a good prognostic indicator of rectal cancer. Ann Nucl Med 2002;16:409–416.
- O'Neill BD, Brown G, Heald RJ, Cunningham D, Tait DM. Non-operative treatment after neoadjuvant chemoradiotherapy for rectal cancer. Lancet Oncol 2007;8(7):625–633.

- Ota DM, Jacobs L, Kuvshinoff B. Rectal cancer: the sphincter-sparing approach. Surg Clin North Am 2002;82(5):983-993.
- Ouchi K, Sugawara T, Ono H, et al. Histologic features and clinical significance of venous invasion in colorectal carcinoma with hepatic metastasis. Cancer 1996;78:2313-2317.

- Padhani AR, Liu G, Koh DM et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11:102–125.
- Pahlman L, Glimelius B. The value of adjuvant radio(chemo)therapy for rectal cancer. Eur J Cancer 1995;31A:1347–1350.
- Pariente A, Milan C, Lafon J, Faivre J. Colonoscopic screening in first-degree relatives of patients with 'sporadic' colorectal cancer: a case-control study. The Association Nationale des Gastroentérologues des Hôpitaux and Registre Bourguignon des Cancers Digestifs (INSERM CRI 9505). Gastroenterology 1998;115(1):7-12.
- Park MJ, Kim SH, Lee SJ, Jang KM, Rhim H. Locally advanced rectal cancer: added value of diffusion-weighted MR imaging for predicting tumor clearance of the mesorectal fascia after neoadjuvant chemotherapy and radiation therapy. Radiology 2011;260(3):771-780.
- Park YJ, Youk EG, Choi HS et al. Experience of 1446 rectal cancer patients in Korea and analysis of prognostic factors. Int J Colorectal Dis 1999;14:101–106.
- Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49(1):33-64.
- Patterson DM, Padhani AR, Collins DJ. Technology insight: water diffusion MRI—a potential new biomarker of response to cancer therapy. Nat Clin Pract Oncol 2008;5:220–233.
- Peeters KC, van de Velde CJ, Leer JW, et al: Late side effects of short course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: Increased bowel dysfunction in irradiated patients—A Dutch colorectal cancer group study. J Clin Oncol 2005;23:6199-6206.
- Pegios W, Vogl J, Mack MG, et al. MRI diagnosis and staging of rectal carcinoma. Abdom Imaging 1996;21:211–218.
- Pema PJ, Bennett WF, Bova JG et al. CT vs MRI in diagnosis of recurrent rectosigmoid carcinoma. J Comp Assist Tomogr 1994;18:256–261.
- Pescatori M, Mattana C, Maria G, Ferrara A, Lucibello L. Outcome of colorectal cancer. Br J Surg 1987;74(5):370-372.
- Peters W, Teixeira M, Intaglietta M, Gross JF. Microcirculation in rat mammary carcinoma. Proc Am Assoc Cancer Res 1980;21:38.
- Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: II. The rectum and rectosigmoid. Br J Surg. 1984 Jan;71(1):17-20.
- Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003;349(23):2191-2200.
- Pomerri F, Pucciarelli S, Maretto I, et al. Prospective assessment of imaging after preoperative chemoradiotherapy for rectal cancer. Surgery 2011;149:56-64.
- Ponz de Leon M, Scapoli C, Zanghieri G, Sassatelli R, Sacchetti C, Barrai I. Genetic transmission of colorectal cancer: exploratory data analysis from a population based registry. J Med Genet 1992;29(8):531-538.
- Potter JD. Colorectal cancer: molecules and populations. J Natl Cancer Inst 1999;91(11):916-932.
- Probst-Hensch NM, Sinha R, Longnecker MP, et al. Meat preparation and colorectal adenomas in a large sigmoidoscopy-based case-control study in California (United States). Cancer Causes Control. 1997;8(2):175-183.
- Puppa G, Maisonneuve P, Sonzogni A, et al. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging, Mod Pathol 2007;20(8):843–855.

- Quasar Collaborative Group, Gray R, Barnwell J, et al: Adjuvant chemotherapy versus observation in patients with colorectal cancer: A randomised study. Lancet 2007;370:2020-2029.
- Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986;2:996–999.
- Quirke P, Steele R, Monson J, et al. MRC CR07/NCIC-CTG CO16 Trial Investigators; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet 2009;373:821–828.

- Rafaelsen SR, Kronborg O, Fenger C. Echo pattern of lymph nodes in colorectal cancer: an in vitro study. Br J Radiol 1992;65:218–220.
- Rao SX, Zeng MS, Chen CZ, et al. The value of diffusion-weighted imaging in combination with T2-weighted imaging for rectal cancer detection. Eur J Radiol 2008;65:299–303.
- Rau B, Hunerbein M, Barth P. Accuracy of endorectal ultrasound after preoperative radiochemotherapy in locally advanced rectal cancer. Surg J Endod 1999;13:980-984.
- Reerink O, Verschueren R, Szabo B et al. A favourable pathological stage after neo-adjuvant radiochemotherapy in patients with initially irresectable rectal cancer correlates with a favourable prognosis. Eur J Cancer 2003;39:1127–1132.
- Registo Oncológico Nacional 2001. Instituto Português de Oncologia de Francisco Gentil, Porto, 2008.
- Registo Oncológico Nacional 2005. Instituto Português de Oncologia de Francisco Gentil, Coimbra, 2009.
- Resch G, de Vries A, Ofner D, et al: Preoperative treatment with capecitabine (C), bevacizumab (B) and radiotherapy (RT) for primary locally advanced rectal cancer (LARC): A two-stage phase II clinical trial. Proceedings of the 2010 ASCO Gastrointestinal Cancers Symposium 2010;(abstr 496).
- Rich T, Gunderson LL, Lew R, Galdibini JJ, Cohen AM, Donaldson G. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983;52:1317-1329.
- Rifkin MD, Ehrlich SM, Marks G: Staging of rectal carcinoma: prospective comparison of endorectal US and CT. Radiology 1989;170:319–322.
- Rigby K, Brown SR, Lakin G, Balsitis M, Hosie KB. The use of a proforma improves colorectal cancer pathology reporting, Ann R Coll Surg Engl, 1999;81(6):401–403.
- Rockey DC, Paulson E, Niedzwiecki D, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet 2005;365(9456):305-311.
- Rodel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688–8696.
- Rodel C, Liersch T, Hermann RM, et al. Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 2007;25:110-117.
- Rosenberg L, Louik C, Shapiro S. Nonsteroidal anti inflammatory drug use and reduced risk of large bowel carcinoma. Cancer 1998;82(12):2326-2333.
- Roth Y, Tichler T, Kostenich G, et al. High-b-value diffusion-weighted MR imaging for pretreatment prediction and early monitoring of tumor response to therapy in mice. Radiology 2004;232:685–692.
- Rotte KH, Kluhs L, Kleinau H, Kriedemann E. Computed tomography and endosonography in the preoperative staging of rectal carcinoma. Eur J Radiol 1989;9:187–190.
- Rozen P, Fireman Z, Figer A, Legum C, Ron E, Lynch HT. Family history of colorectal cancer as a marker of potential malignancy within a screening program. Cancer 1987;60(2):248-254.
- Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. Cancer 2000;89:46-52.
- Rustgi AK. Hereditary gastrointestinal polyposis and nonpolyposis syndromes. N Engl J Med 1994;331(25):1694-1702.

- Sagar PM, Pemberton JH. Surgical management of locally recurrent rectal cancer. Br J Surg 1996;83:293–304.
- Sahani DV, Kalva SP, Hamberg LM, et al. Assessing Tumor Perfusion and Treatment Response in Rectal Cancer with Multisection CT: Initial Observations. Radiology 2005;234:785–792.
- Sailer M, Leppert R, Kraemer M, Fuchs KH, Thiede A. The value of endorectal ultrasound in the assessment of adenomas, T1- and T2-carcinomas. Int J Colorectal Dis 1997;12:214–219.
- Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–1740.
- Schaefer O, Langer M. Detection of recurrent rectal cancer with CT, MRI and PET/CT. Eur Radiol 2007;17:2044–2054.
- Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 2000;342(16):1149-1155.
- Schnall M, Furth EE, Rosato E, Kressel HY: Rectal tumour stage: correlation of endorectal MRI and pathologic findings. Radiology 1994;190:709–714.

- Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant FOLFOX-bev, without radiation, for locally advanced rectal cancer. J Clin Oncol 2010;28:15S-263S,(abstr 3511)
- Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811–820.
- Seierstad T, Roe K, Olsen DR. Noninvasive monitoring of radiation-induced treatment response using proton magnetic resonance spectroscopy and diffusion-weighted magnetic resonance imaging in a colorectal tumor model. Radiother Oncol 2007;85:187–194.
- Seitz HK, Simanowski UA, Garzon FT, et al. Possible role of acetaldehyde in ethanol-related rectal cocarcinogenesis in the rat. Gastroenterology 1990;98(2):406-413.
- Selby JV, Friedman GD, Quesenberry CP, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653-657.
- Sengupta S, Tjandra JJ. Local excision of rectal cancer: what is the evidence? Dis Colon Rectum 2001;44:1345–1361.
- Shank B, Dershaw DD, Caravelli J, Barth J, Enker W. A prospective study of the accuracy of preoperative computed tomographic staging of patients with biopsy-proven rectal carcinoma. Dis Colon Rectum 1990;33:285–290.
- Shepherd NA, Baxter KJ, Love SB. Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer. J Clin Pathol 1995;48:849–855.
- Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. Am J Epidemiol 1998;148(8):761-774.
- Slattery ML, Potter J, Caan B, et al. Energy balance and colon cancer-beyond physical activity. Cancer Res 1997;57(1):75-80.
- Smith N, Brown G. Preoperative staging of rectal cancer. Acta Oncologica 2007;47(1):20—31.
- Smith NJ, Shihab O, Arnaout A et al. MRI for detection of extramural vascular invasion in rectal cancer. AJR Am J Roentgenol 2008;191:1517–1522.
- Solomon MJ, McLeod RS. Endoluminal transrectal ultrasonography: accuracy, reliability, and validity. Dis Colon Rectum 1993;36:200–205.
- Solomon MJ, McLeod RS, Cohen EK, Simons ME, Wilson S. Reliability and validity studies of endoluminal ultrasonography for anorectal disorders. Dis Colon Rectum 1994;37:546–551.
- Spirio L, Olschwang S, Groden J, et al. Alleles of the APC gene: an attenuated form of familial polyposis. Cell 1993;75(5):951-957.
- Starck M, Bohe M, Fork FT, Lindstrom C, Sjoberg S. Endoluminal ultrasound and low-field magnetic resonance imaging are superior to clinical examination in the preoperative staging of rectal cancer. Eur J Surg 1995;161:841–845.
- Stein W, Farina A, Gaffney K, Lundeen C, Wagner K, Wachtel T. Characteristics of colon cancer at time of presentation. Fam Pract Res J 1993;13(4):355-363.
- Steup WH, Moriya Y, van de Velde CJ. Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. Eur J Cancer 2002;38:911–918.
- St Lawrence KS, Lee TY. An adiabatic approximation to the tissue homogeneity model for water exchange in the brain. I. Theoretical derivation. J Cereb Blood Flow Metab 1998;18:1365–1377.
- Stoker J, Rociu E, Wiersma TG et al. Imaging of anorectal disease. Br J Surg 2000;87:10–27.
- Stueckle CA, Haegele KF, Jendreck M et al. Improvements in detection of rectal cancer recurrence by multiplanar reconstruction. Radiologe 2005;45:930–935.
- Stueckle CA, Adams S, Stueckle KF et al. Multi-detector CT in the evaluation of patients with recurrence of rectal cancer. Technol Cancer Res Treat 2006;5:285–289.
- Summers RM, Yao J, Pickhardt PJ, et al. Computed tomographic virtual colonoscopy computer-aided polyp detection in a screening population. Gastroenterology 2005;129(6):1832-1844.
- Sun YS, Zhang XP, Tang L et al. Locally advanced rectal carcinoma treated with preoperative chemotherapy and radiation therapy: preliminary analysis of diffusion-weighted MR imaging for early detection of tumor histopathologic downstaging. Radiology 2010:254:170–178.
- Suppiah A, Hunter IA, Cowley J, et al. Magnetic resonance imaging accuracy in assessing tumour down-staging following chemoradiation in rectal cancer. Colorectal Dis 2009;11:249–253.
- Suzuki K, Muoto T, Sawada T. Prevention of local recurrence by extended lymphadenectomy for rectal cancer. Surg Today 1995;25:795–801.
- Swedish Rectal Cancer Trial [see Comments]. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980–987 [erratum, N Engl J Med 1997;336:1539].
- Syk E, Torkzad MR, Blomqvist L, Nilsson PJ, Glimelius B. Local recurrence in rectal cancer: anatomic localization and effect on radiation target. Int J Radiat Oncol Biol Phys 2008;72:658–664.

- Takahara T, Imai Y, Yamashita T, Yasuda S, Nasu S, Van Cauteren M. Diffusion weighted whole body imaging with background body signal suppression (DWIBS): technical improvement using free breathing, STIR and high resolution 3D display. Radiat Med 2004;22(4):275–282.
- Takahashi T, Ueno M, Azekura K et al. Lateral node dissection and total mesorectal excision for rectal cancer. Dis Colon Rectum 2000;43:59–68.
- Takeuchi O, Saito N, Koda K, Sarashina H, Nakajima N. Clinical assessment of positron emission tomography for the diagnosis of local recurrence in colorectal cancer. Br J Surg 1999;86:932–937.
- Talbot IC, Ritchie S, Leighton MH et al. The clinical significance of invasion of veins by rectal cancer. Br J Surg 1980;67:439–442.
- Tang R, Wang JY, Chen JS et al. Survival impact of lymph node metastasis in TNM stage III carcinoma of the colon and rectum. J Am Coll Surg 1995;180:705–712.
- Tanoura T, Bernas M, Darkazanli A, et al. MR lymphography with iron oxide compound AMI-227: studies in ferrets with filiariasis. AJR Am J Roentgenol 1992;159:875-881.
- Taylor A, Sheridan M, McGee S, Halligan S. Preoperative staging of rectal cancer by MRI; results of a UK survey. Clin Radiol 2005;60:579–586.
- Taylor FG, Quirke P, Heald R, et al.; on behalf of the MERCURY study group. MRI prediction of surgical margin status in rectal cancer. 1 mm is the safe cut off. Abstracts of the Fourth Annual Meeting of the European Society of Coloproctology. September 23 – 26, 2009. Prague, Czech Republic. Colorectal Dis 2009;11(Suppl 2):1–57.
- Taylor FGM, Quirke P, Heald RJ et al. One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer. British Journal of Surgery 2011;98:872–879.
- Taylor SA, Halligan S, Saunders BP, Bassett P, Vance M, Bartram CI. Acceptance by patients of multidetector CT colonography compared with barium enema examinations, flexible sigmoidoscopy, and colonoscopy. AJR Am J Roentgenol 2003a;181(4):913-921.
- Taylor SA, Halligan S, O'Donnell C, et al. Cardiovascular effects at multi-detector row CT colonography compared with those at conventional endoscopy of the colon. Radiology 2003b;229(3):782-790.
- Taylor SA, Halligan S, Burling D, Bassett P, Bartram CI. Intra-individual comparison of patient acceptability of multidetector-row CT colonography and double-contrast barium enema. Clin Radiol 2005;60(2):207-214.
- Taylor SA, Halligan S, Burling D, et al. Computer-assisted reader software versus expert reviewers for polyp detection on CT colonography. AJR Am J Roentgenol 2006;186(3):696-702.
- Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: Analysis of stage, sex, and local control—Final report of Intergroup 0114. J Clin Oncol 2002;20:1744-1750.
- Thaler W, Watzka S, Martin F, et al. Preoperative staging of rectal cancer by endoluminal ultrasound vs. magnetic resonance imaging. Preliminary results of a prospective, comparative study. Dis Colon Rectum 1994;37(12):1189–1193.
- Theilmann RJ, Borders R, Trouard TP, et al. Changes in water mobility measured by diffusion MRI predict response of metastatic breast cancer to chemotherapy. Neoplasia 2004;6:831–837.
- Theodoropoulos G, Wise WE, Padmanabhan A, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002;45:895–903.
- Thoeni RF, Moss AA, Schnyder P, Margulis AR. Detection and staging of primary rectal and rectosigmoid cancer by computed tomography. Radiology 1981;141:135–138.
- Thoeni RF. CT evaluation of carcinomas of the colon and rectum. Radiol Clin North Am 1989;27:731–774.
- Thoeny HC, De Keyzer F, Chen F, et al. Diffusion-weighted MR imaging in monitoring the effect of a vascular targeting agent on rhabdomyosarcoma in rats. Radiology 2005;234(3):756–764.
- Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991;325(23):1593-1596.
- Tinetti ME, Stone L, Cooney L et al. Inadequate barium enema in hospitalized elderly patients. Incidence and risk factors. Arch Intern Med 1989;149:2014–2016.
- Tiret E, Poupardin B, McNamara D, Dehni N, Parc R. Ultralow anterior resection with intersphincteric dissection-what is the limit of safe sphincter preservation? Colorectal Dis 2003;5(5):454-457.
- Titu LV, Nicholson AA, Hartley JE, Breen DJ, Monson JR. Routine follow-up by magnetic resonance imaging does not improve detection of resectable local recurrences from colorectal cancer. Ann Surg 2006;243:348–352.

- Torricelli P, Pecchi A, Luppi G, Romagnoli R. Gadolinium-enhanced MRI with dynamic evaluation in diagnosing the local recurrence of rectal cancer. Abdom Imaging 2003;28:19–27.
- Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ 1998;317(7158):559-565.
- Tsang WW, Chung CC, Li MK. Prospective evaluation of laparoscopic total mesorectal excision with colonic J-pouch reconstruction for mid and low rectal cancers. Br J Surg 2003;90(7):867-871.

- Ueno H, Mochizuki H, Hashiguchi Y et al. Prognostic determinants of patients with lateral nodal involvement by rectal cancer. Ann Surg 2001;234:190–197.
- Urban M, Rosen HR, Holbling N, et al. MR imaging for the preoperative planning of sphincter-saving surgery for tumors of the lower third of the rectum: use of intravenous and endorectal contrast materials. Radiology 2000;214(2):503–508.

- Valentini V, Coco C, Cellini N, et al. Preoperative chemoradiation for extraperitoneal T3 rectal cancer: acute toxicity, tumor response, and sphincter preservation. Int J Radiat Oncol Biol Phys 1998;40(5):1067–1075.
- Valentini V, Coco C, Picciocchi A, et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 2002;53:664–674.
- Valentini V, Aristei C, Glimelius B, et al. Multidisciplinary rectal cancer management: 2nd european rectal cancer consensus conference (EURECA-CC2). Radiother Oncol 2009;92:148–163.
- Vanagunas A, Lin DE, Stryker SJ. Accuracy of endoscopic ultrasound for restaging rectal cancer following neoadjuvant chemoradiation therapy. Am J Gastroenterol 2004;99:109–112.
- Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-1664.
- Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-1417.
- Vandecaveye V, De Keyzer F, Nuyts S, et al. Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo)radiotherapy: correlation between radiologic and histopathologic findings. Int J Radiat Oncol Biol Phys 2007;67:960–971.
- Van der Brekel MW, Stel HV, Castelijns JA, et al. Cervical lymph node metastasis: assessment of radiologic criteria. Radiology 1990;177:379-384.
- Van Waes PF, Koehler PR, Feldberg MA. Management of rectal carcinoma: impact of computed tomography. AJR Am J Roentgenol 1983;140:1137–1142.
- Varma MG, Rogers SJ, Schrock TR, Welton ML. Local excision of rectal carcinoma. Arch Surg 1999;134:863–867.
- Villa E, Dugani A, Rebecchi AM, et al. Identification of subjects at risk for colorectal carcinoma through a test based on K-ras determination in the stool. Gastroenterology 1996;110(5):1346-1353.
- Vining DJ, Gelfand DW, Bechtold RE, et al. Technical feasibility of colon imaging with helical CT and virtual reality. AJR Am J Roentgenol 1994;162:Suppl,104.
- Vliegen RF, Beets GL, von Meyenfeldt MF, et al: Rectal cancer: MRI in local staging-is gadolinium-based contrast material helpful? Radiology 2005;234:179–188.
- Vliegen R, Dresen R, Beets G, et al. The accuracy of Multi-detector row CT for the assessment of tumor invasion of the mesorectal fascia in primary rectal cancer. Abdom Imaging 2008a;33:604–610.
- Vliegen RF, Beets GL, Lammering G, et al. Mesorectal fascia invasion after neoadjuvant chemotherapy and radiation therapy for locally advanced rectal cancer: accuracy of MR imaging for prediction. Radiology 2008b;246:454–462.
- Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal tumor development. N Engl J Med 1988;319:525-532.
- Vogl TJ, Pegios W, Mack MG, et al. Accuracy of staging rectal tumors with contrast-enhanced transrectal MR imaging. AJR Am J Roentgenol 1997;168:1427–1434.
- Vogl TJ, Pegios W, Hunerbein M, Mack MG, Schlag PM, Felix R. Use and applications of MRI techniques in the diagnosis and staging of rectal lesions. Recent Results Cancer Res 1998;146:35–47.
- Von Schulthess GK, Steinert HC, Hany TF. Integrated PET/CT: current applications and future directions. Radiology 2006;238:405–422.

- Wang C, Zhou Z, Wang Z, et al. Patterns of neoplastic foci and lymph node micrometastasis within the mesorectum. Langenbecks Arch Surg 2005;390:312–318.
- Wargovich MJ. New dietary anticarcinogens and prevention of gastrointestinal cancer. Dis Colon Rectum 1988;31(1):72-75.
- Weissleder R, Elizondo G, Wittenberg J, Lee A, Josephson L, Brady T. Ultrasmall superparamagnetic iron oxide: an intravenous contrast agent for assessing lymph nodes with MR imaging. Radiology 1990;175; 494-498.
- Wheeler RH, Ziessman HA, Medvec BR, et al. Tumor blood flow and systemic shunting in patients receiving intraarterial chemotherapy for head and neck cancer. Cancer Res 1986;46:4200–4204.
- Whittemore AS, Wu-Williams AH, Lee M, et al. Diet, physical activity, and colorectal cancer among Chinese in North America and China. J Natl Cancer Inst 1990;82(11):915-926.
- Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg 2002;89:327–334.
- Wieder HA, Rosenberg R, Lordick F, et al. Rectal cancer: MR imaging before neoadjuvant chemotherapy and radiation therapy for prediction of tumor-free circumferential resection margins and long-term survival. Radiology 2007;243:744–751.
- Will O, Purkayastha S, Chan C, et al. Diagnostic precision of nanoparticle-enhanced MRI for lymph-node metastases: a meta-analysis. Lancet Oncol 2006;7:52–60.
- Willett CG, Badizadegan K, Ancukiewicz M et al. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167–173.
- Willett CG. Sphincter preservation in rectal cancer. Curr Treat Options Oncol 2000;1(5):399-405.
- Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: A multidisciplinary phase II study. J Clin Oncol 2009;27:3020-3026.
- Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990;323(24):1664-1672.
- Williams AD, Cousins C, Soutter WP, et al. Detection of pelvic lymph node metastases in gynecologic malignancy: a comparison of CT, MR imaging, and positron emission tomography. AJR Am J Roentgenol 2001;177:343–348.
- Wilmink AB. Overview of the epidemiology of colorectal cancer. Dis Colon Rectum 1997;40(4):483-493.
- Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale – update based on new evidence. Gastroenterology 2003;124:544-560.
- Winawer SJ, Zauber AG, Gerdes H, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. N Engl J Med 1996;334(2):82-87.
- Winawer SJ, Stewart ET, Zauber AG, et al. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. N Engl J Med 2000;342(24):1766-1772.
- Winde G, Nottberg H, Keller R, Schmid KW, Bunte H. Surgical cure for early rectal carcinomas (T1): transanal endoscopic microsurgery vs anterior resection. Dis Colon Rectum 1996;39:969–976.
- Wolberink S, Beets-Tan RG, de Haas-Kock D, et al. Conventional CT for the prediction of an involved circumferential resection margin in primary rectal cancer. Dig Dis 2007;25:80–85.
- Wolmark N, Fisher B, Wieand HS. The prognostic value of the modifications of the Dukes' C class of colorectal cancer: an analysis of the NSABP clinical trials. Ann Surg 1986;203:115–122.
- Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorinmodulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: Results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993;11:1879-1887.
- Wolmark N, Wieand S, Kuebler PJ, et al. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Survival results of NSABP Protocol C-07. J Clin Oncol 2008;26,15S.
- Woodhams R, Kakita S, Hata H, et al. Diffusion-weighted imaging of mucinous carcinoma of the breast: evaluation of apparent diffusion coefficient and signal intensity in correlation with histologic findings. AJR Am J Roentgenol 2009;193:260–266.
- Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL. Calcium intake and risk of colon cancer in women and men. J Natl Cancer Inst 2002;94(6):437-446.

- Zagoria RJ, Schlarb CA, Ott DJ, et al. Assessment of rectal tumor infiltration utilizing endorectal MR imaging and comparison with endoscopic rectal sonography. J Surg Oncol 1997;64:312–317.
- Zaunbauer W, Haertel M, Fuchs WA. Computed tomography in carcinoma of the rectum. Gastrointest Radiol 1981;6:79–84.
- Zerhouni EA, Rutter C, Hamilton SR, et al. CT and MR imaging in the staging of colorectal carcinoma: report of the Radiology Diagnostic Oncology Group II. Radiology 1996;200:443–451.
- Zhou ZG, Wang Z, Yu YY, et al. Laparoscopic total mesorectal excision of low rectal cancer with preservation of anal sphincter: a report of 82 cases. World J Gastroenterol 2003;9(7):1477-1481.