Challenges in the Multimodality Treatment of Rectal Cancer

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Ter nagedachtenis
aan mijn vader

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CHAPTER 1

Introduction

INTRODUCTION

EPIDEMIOLOGY

Colorectal cancer is the second most frequent cancer among females after breast cancer and the third most common cancer among males, after prostate and lung cancer[1]. In 2010, 12755 patients were diagnosed with colorectal cancer in the Netherlands. Of these, 3667 (29%) were located in the rectum[2]. The incidence is rising, partly due to growth and ageing of the population.

Rectal cancer is associated with a relatively poor prognosis due to the high risk of local recurrence and distant metastases. After 5 years, approximately 60% of patients are still alive. The diagnosis and optimal treatment of rectal cancer is a multidisciplinary team effort made by the gastroenterologist, radiologist, radiation oncologist, medical oncologist, surgeon and pathologist. In the past two decades our understanding of the locoregional spread of rectal cancer has improved substantially leading to major improvements in preoperative staging, surgical technique, histopathological aspects and to the introduction of preoperative (chemo)radiotherapy. This has decreased local recurrence (LR) rates from 15-45% to approximately 10%. Distant metastases occurring in 20%-30% of patients have now become the event determining outcome which requires priority in future research.

DEFINITION OF THE RECTUM

Anatomically, the rectum emerges from the sigmoid colon about 12-15 cm from the anal verge (illustrated in Figure 1), where it curves posteriorly and descends within the bony pelvis. The rectum is surrounded by a fatty envelop, the mesorectum. At about 2-3 cm from the anal verge the levator muscle complex cones in and closely encases the rectum, replacing the fatty mesorectum. The mesorectum contains a powerful prognosticator in rectal cancer, the regional lymph nodes, and is circumferentially enclosed by the mesorectal fascia (MRF) (illustrated in Figure 2). Regarding the lymph drainage, the upper rectum drains into the inferior mesenteric system, while the middle and lower rectum may also drain directly into other lymph node stations, for example the internal iliac or the presacral nodes.

DEFINITION OF LOCALLY ADVANCED RECTAL CANCER

About 10% of patients present themselves at a later stage with more advanced locoregional disease, termed locally advanced rectal cancer (LARC): the tumour threatens or invades the MRF, sometimes even infiltrating surrounding structures and organs, and (more) pathologic lymph nodes may have developed (illustrated in Figure 2). The definition of locally advanced rectal cancer varies in the literature and differs in different geographical regions. Generally, North-Western Europe[1;3] reserves this definition for only those “ugly” tumours threatening or invading the MRF, invading surrounding organs, those with more than 3 mesorectal lymph node metastases or with enlarged lateral pelvic lymph nodes. In Mediterranean countries[4-6] and the US[7;8] the definition is applied less vigorously and includes all tumours invading the mesorectal fat or surrounding organs, or with one or more nodal metastases.

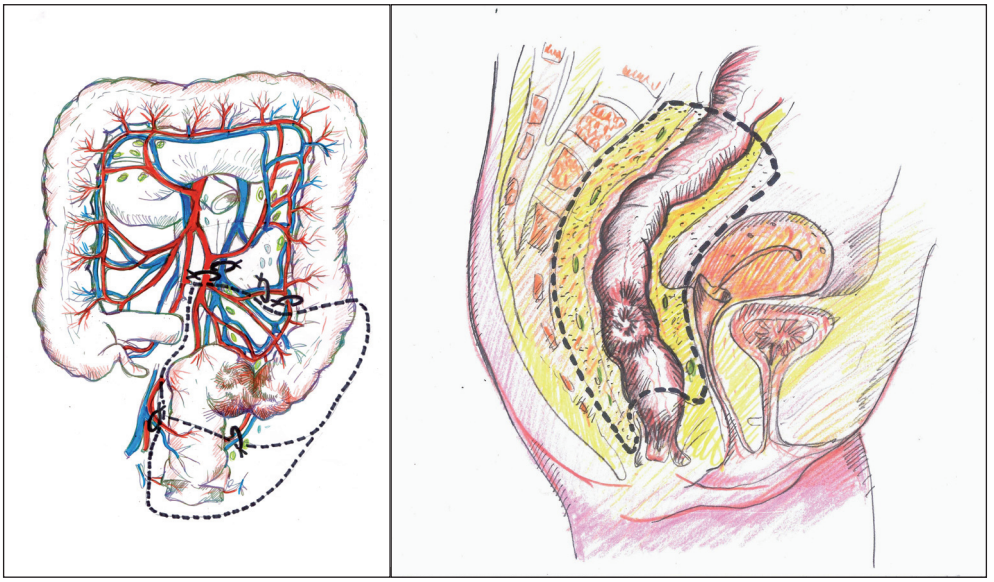

Figure 1: the left drawing depicts the gastrointestinal tract starting with the stomach, which becomes the small intestine (removed in this illustration), the colon and then the rectum and anus. Dotted lines depict two areas: the upper area is resected during a low anterior resection, implemented for mid and upper rectal tumours. In case of a low rectal tumour, situated close to the anal sphincter, an abdominoperineal resection is performed whereby both areas are resected. The right drawing shows a sagittal or lateral view of the female rectum, enveloped by the mesorectal fat tissue. Dotted lines depict the plane of resection during a low anterior resection according to the principles of total mesorectal excision. Lymph nodes are coloured in green. Drawings by H. van't Hof.

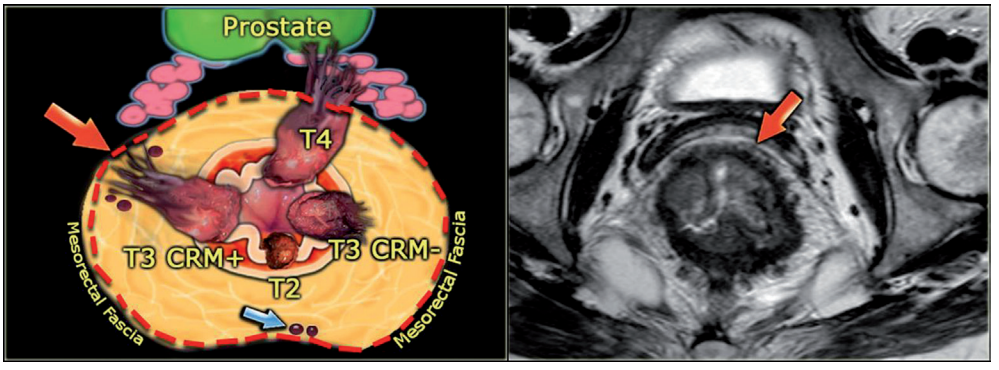

Figure 2: On the left a schematic representation of an axial image of the rectum of a male, showing 4 examples of primary tumour growth: a clinical T2 (cT2) tumour which stays confined to the muscular layer, a cT3 that invades the mesorectal fat and does (red arrow) or does not threaten the mesorectal fascia (MRF) or a cT4 tumour which invades the prostate. The red dotted line shows the MRF along which total mesorectal excision (TME) is performed. The blue arrow demonstrates pathologically enlarged mesorectal lymph nodes. On the right a slice of magnetic resonance imaging (MRI) depicting a tumour with infiltration of the MRF on the anterior side (red arrow). This tumour is classified as a cT3 with an involved MRF, thereby classifying it as a locally advanced tumour requiring preoperative chemoradiotherapy. Reprinted with permission from Robin Smithuis, RadiologyAssistant.nl. © 2013.

PREOPERATIVE STAGING

Preoperative staging of rectal cancer is an important aspect of clinical management, particularly in determining indications for neoadjuvant therapy. Diagnosis of rectal cancer follows after pathological confirmation of biopsies taken from the tumour during endoscopy. The height of the tumour can be estimated from the anal verge which aids the choice in type of surgical resection. The classical way to evaluate the extent of a rectal tumour is by digital rectal examination (DRE). However, clinical terms such as fixed or mobile are difficult to interpret and inter-observer bias is high. Furthermore, information gained with DRE does not reflect the relationship between the tumour and the underlying structures like the mesorectal fascia. Therefore, further imaging of the pelvis to stage local disease follows, whereby depth of primary tumour invasion (T-stage) and the presence of lymph node metastases (N-stage) are important factors[9]. Regarding the accuracy of the different staging tools at hand, Bipat[10] reported the results of a meta-analysis of 90 studies investigating staging accuracy. In summary, endoluminal-ultrasound (EUS) has an important role in the staging of superficial tumours and is preferred over MRI to differentiate between T1 and T2 tumours. The abdominal multi-slice CT was traditionally implemented for more locally advanced tumours but following improvements in resolution of the MRI, the MRI has now become the cornerstone of staging for non-superficial rectal cancer (cT3-4) giving more information, in addition to tumour depth and height. Advantages of the MRI include the ability to visualize the relationship between the tumour and the MRF (illustrated in Figure 2) and predict MRF involvement accurately[11;12]. This relationship affects preoperative treatment planning significantly, enabling a more patient tailored approach. The preoperative identification of lymph node metastases is difficult but improvements have been made with the introduction of the MRI, whereby size, inhomogeneity and border contour seem to be predictive factors[13]. However, nodal staging remains unreliable and is in need of further development in the future. Another recent and promising finding is the ability to identify extra-mural vascular invasion of the tumour on MRI[14], which has proven to be a prognostic factor predicting locally advanced disease and associated poor outcome. However, more evidence is required to embed this factor into standard MRI staging in daily clinical practice and the definition of LARC.

Another important aspect of preoperative staging involves screening of systemic dissemination. A CT-scan of the abdomen or ultrasound of the liver, and X-ray or CT-scan of the thorax can evaluate the occurrence of distant metastases, at diagnosis and during follow-up. Positron emission tomography (PET) using 18-flurodeoxyglucose tracer is increasingly being applied to evaluate metastatic or recurrent disease but presently has no role in initial preoperative staging[15]. As resolution improves and combinations between imaging modalities become possible (like PET-MRI) staging will become more complex and expensive, but hopefully lead to more accuracy.

IMPROVEMENTS IN SURGICAL TECHNIQUE

Surgery remains the cornerstone of rectal cancer treatment. Up to the early 1990's, population-based and randomized studies reported LR rates up to 45% after conventional "blunt" surgery[16]. Heald was the first European surgeon to publish superior local control resulting from a new surgical technique: total mesorectal excision (TME)[17]. He acknowledged the importance of the mesorectum by incorporating embryologically determined planes into surgery. Instead of the blunt dissection of the perirectal fascia, he advocated sharp dissection under direct vision of the "holy plane", an avascular plane formed by the mesorectal fascia. In doing so the surgeon provided the pathologist with a surgical specimen with an intact mesorectum, as illustrated in Figure 3, resulting in a lower rate of positive resection margins. Additionally, the pelvic autonomous nerves could be spared, thereby reducing urinary and sexual dysfunction. Heald[18] reported a LR rate of 6% after 5 years and this was confirmed by other single-centre series like Enker *et al*[19] reporting a LR rate of 7%. These clearly superior results led to the consensus-based introduction of TME as standard of care in rectal cancer without awaiting further evidence from a randomized study.

The Dutch TME trial[20] was designed in the Netherlands as part of a nationwide initiative to introduce TME and optimize and standardize treatment of rectal cancer. Workshops were held and instructor surgeons were appointed to teach fellow surgeons. A total of 1861 patients were included between 1996 and 1999 and quality of surgery and pathology was studied and assured. Results confirmed low LR rates of 11% after TME alone with a negative CRM being a powerful predictor. An APR was also associated with a higher LR rate compared to a low anterior resection (LAR). In-depth analysis demonstrated that an APR was associated with a higher CRM positive rate of 30%[21], probably due to the fact that anatomically, the mesorectal fat disappears in the distal rectum, misleading the surgeon to "cone in" and cause a positive margin. This has led to a change in surgical approach for distal rectal cancer by maintaining a "cylindrical" resection distal from the levator muscles to retain adequate circumferential margins. Overall, the introduction and training of TME over the years has decreased LR after 2 years (after TME only) from 16% to 9% and increased overall survival from 77% to 86% in the Netherlands[22].

DEVELOPMENTS IN (NEO)ADJUVANT STRATEGIES

In the last decades, perioperative or (neo)adjuvant treatments have been added to the surgical treatment of rectal cancer to further improve prognosis. At present preoperative or neoadjuvant therapy is given with two goals in mind: short-course radiotherapy (SCRT, 5x5 Gy), for the eradication of pelvic micro-metastases which is followed directly by TME, and long-course chemoradiotherapy (CRT) for downsizing of locally advanced tumours to facilitate radical resection 6-8 weeks later. To understand these two goals the important studies responsible for their introduction are discussed in the next paragraph.

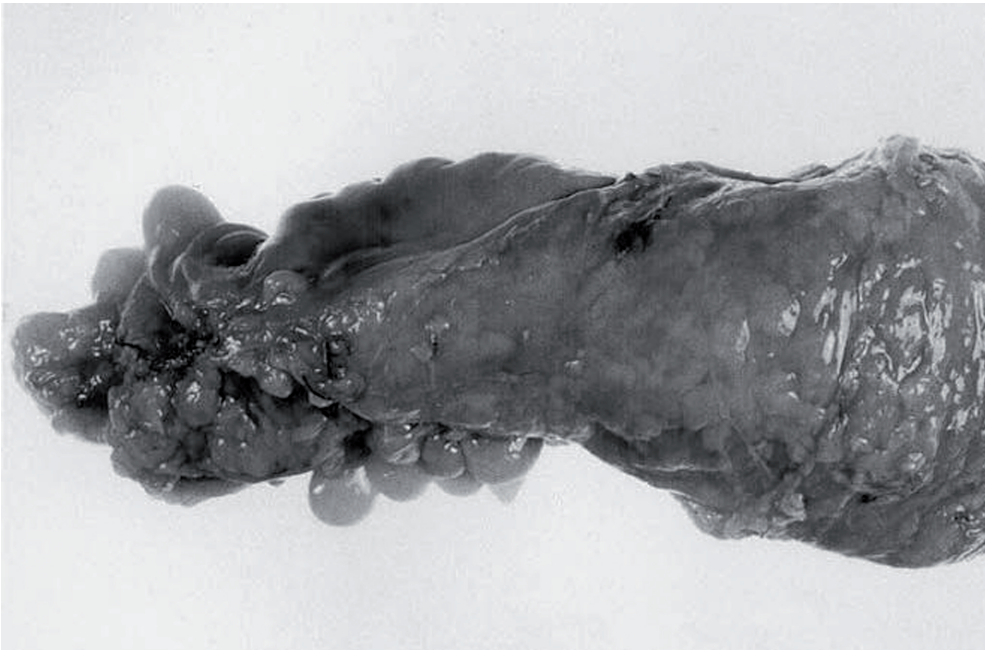

Figure 3 depicts a macroscopic complete rectal resection specimen after TME surgery. Reprinted with permission

The Swedish Rectal Cancer Trial[24] which included patients in the pre-TME era, showed that SCRT administered 1 week prior to conventional surgery was capable of reducing 5-year local recurrence rates (27% vs. 11%) and improving 5-year overall survival (48% vs. 58%) compared with conventional (non-TME) surgery alone. After a median of 13 years these differences maintained significance[25]. The abovementioned Dutch TME trial followed with a similar design and investigated the additive value of this regimen when TME surgery was performed. It confirmed that neoadjuvant SCRT decreased the long-term LR rates from 11% with TME surgery only, to 6% after 5x5 Gy RT and TME, but found no difference in survival[26]. An important finding was that SCRT followed directly by TME does not compensate for tumour positive resection margins[27]. Patients at risk for a positive CRM should therefore be selected preoperatively to achieve preoperative downsizing of the tumour with a conventional radiotherapy schedule in order to facilitate radical surgery. In patients with LARC, the addition of chemotherapy to long-course radiotherapy (CRT, 45-50 Gy) followed by delayed surgery results in increased downsizing and downstaging and a reduction in local recurrences compared with either neoadjuvant radiation without chemotherapy or CRT delivered in the postoperative setting[4;28-30]. However, no effect on overall survival was found in any of these studies. Two studies, a Polish and an Australian randomized trial, later compared CRT followed by delayed TME and SCRT followed by direct TME in resectable rectal cancer and observed more downstaging after CRT, but found no significant difference in local recurrence, DFS or OS[31;32]. However, both studies were underpowered, making it difficult to draw firm conclusions. To answer the question

whether delaying TME after SCRT will facilitate downstaging, the Stockholm III trial is presently randomizing patients between SCRT followed by direct TME, delayed TME or long-course RT and delayed TME.

Other on-going discussions over future neoadjuvant strategies include whether an increase in tumour response should be a goal of research. Ways do attain this would be to increase total dose of radiotherapy, for instance by using an integrated boost or brachytherapy, or by adding other (combinations of) chemoradiosensitizers to the radiotherapy to optimize response to radiotherapy. However, the latter seems to increase toxicity without significant increases in response[33]. Lastly, one could intensify the role of chemotherapy, for instance by starting with neoadjuvant chemotherapy, followed by SCRT or CRT and delayed surgery. A possible reason to increase response would be to be able to limit surgical intervention necessary for cure, a concept discussed in the following paragraph.

MODERN ORGAN-PRESERVING APPROACHES

After TME, whether an APR or LAR is performed, life-altering changes in (bowel) function, with or without a stoma, occur which affect quality of life. As a result there is an active interest in applying less invasive methods for management of rectal cancer, but oncological safety must be guaranteed.

Local excision has been investigated in the treatment of early rectal cancer. Recent reports of stage T1N0 rectal tumours resected using transanal endoscopic microsurgery (TEM), instead of a TME, indeed show lower rates of morbidity and mortality, but at a cost of increased local recurrence rates of more than 20%[34;35]. Of note, salvage surgery for these patients and survival upon diagnosis of a local recurrence proved to be dismal due to the development of distant metastases in 39%[36] and emphasize potential dangers of less invasive surgical treatment.

In a German randomized trial investigating the treatment of cT3-4 or node-positive disease, all patients undergoing neoadjuvant CRT and TME 6 weeks later were evaluated for response to therapy. Ten percent of patients had a pathologic complete response (pCR) with no viable tumour identified after resection[30]. No patients with a pCR developed local recurrence of disease, and these patients experienced superior disease-free survival than did those with a lesser response to neoadjuvant therapy. In the literature pCR rates of up to 30% have been described with subsequent excellent outcome[6;37;38] which has led to investigations into a non-operative `wait and see` policy[37]. Assessment of clinical response is done using digital and endoscopic rectal examination with biopsies taken from suspicious areas, CT scan of the abdomen and EUS, whereby patients showing a clinical complete response are selected for less invasive surgery or omission of surgery all together. These patients are monitored in an intensified follow up scheme. Habr-Gama *et al*[39] have published encouraging results after omitting TME, which have been confirmed by another smaller series[40]. However, concerns have been expressed by others[41] demonstrating that only 30% of patients with a clinical complete response actually have a pCR. Advanced imaging techniques, such as diffusion weighted MRI[42] might improve accuracy. The data on this interesting topic is sparse and limited to single centres and together with the inaccuracy of standard imaging tools to assess response and nodal disease, needs further

validation. Another option consisting of full thickness TEM in responding tumours after CRT, has recently gathered interest with advantages of tissue sampling for valuable histopathological analysis and results in acceptable short-term local control rates [43;44].

Long-term outcome will determine possible indications for these conservative approaches as potential tumour deposits or lymph node metastases in the mesorectum are not assessed or treated in this way and may affect prognosis drastically. The importance of clinically undetectable residual tumour deposits in the mesorectum has not yet been clarified. The risk of lymph node involvement increases with depth of wall penetration. In a population based study of non-irradiated patients, lymph node involvement was observed in 6-14% of T1 tumours, in 17% to 23% ofT2 tumours, and in 49% to 66% of T3 tumours, respectively[45]. In a series of 121 patients receiving neoadjuvant CRT[46], lymph node metastases occurred in 8% in ypT0, 0% in ypT1, 19% in ypT2, 49% in ypT3 and 75% in ypT4 disease. The risks of under-treatment and subsequent residual disease require further investigation before one can safely embark local excision policies. On the other hand overtreatment of those unresponsive to CRT, resulting in unnecessary toxicity, is also an issue.

DEMARCATION OF TUMOURS IN THE RECTUM

External beam radiotherapy is the "main delivery technique" in radiotherapy. Endorectal brachytherapy, a promising new option based on contact x-ray therapy as described in the early 1970's, is given through a flexible multi-channel applicator placed in the rectum. Utilizing their radiopaque characteristics, endoclips have been used to mark tumours or anatomical structures to facilitate intervention radiology[47] and radiotherapy[48;49] or to locate the tumour intra-operatively[50]. A modern indication is the use to aid correct positioning of the endorectal applicator, for tumour location but also for target volume delineation purposes during brachytherapy. Furthermore, as CRT results in complete remission in up to 30% of patients, demarcation of the tumour location will become more important in the future. Different types of clips have been developed which facilitate a better grasp of the tissue thereby probably improving retention rates. Retention rates have, however, only been evaluated in canines and pigs and have not yet been reported in the human gastrointestinal tract.

ADVERSE EFFECTS ASSOCIATED WITH THE TREATMENT OF RECTAL CANCER

As prognosis of rectal cancer treatment improves, adverse effects and quality of life become more important issues that need to be weighed up against potential advantages resulting from the different improvements. Adverse effects of surgery include surgical complications and long-term pelvic organ dysfunction while adverse effects of (C)RT include short- and long-term toxicity. The combined modality treatment causes mixed and sometimes additive toxicity.

A symptomatic anastomotic leakage after a LAR, which is the most feared complication, occurs in 10%[51] and can lead to abdominal sepsis and even death, while intra-abdominal abscesses delay postoperative recovery. In a Swedish randomized controlled trial, a deviating stoma after LAR decreased the number of symptomatic anastomotic leakages from 28% to 10%[52]. However, stoma reversal is also

associated with morbidity and mortality[53] and is not possible in a fifth of patients[54]. Perineal wound complications after abdominoperineal resection (APR) occur in up to 34%[55] of patients and represent a challenging management problem, with associated pain, unpleasant odour and unexpected drainage seriously affecting quality of life. After neoadjuvant CRT, anastomotic leak rates of up to 27% have been reported[55], but this has not been reproduced in the randomized controlled trials[4;30;56]. However, complication rates are not endpoints of randomized controlled trials and definitions used for scoring complications are seldomly reported in retrospective series, which indicate lack of actual complication rates after CRT followed by delayed TME.

With regards to long-term adverse effects of surgery and subsequent quality of a life, a recent comparative study found APR to be comparable to LAR, with 72% of LAR patients experiencing a degree of faecal incontinence while sexual dysfunction was higher in the APR group[57]. An analysis of long-term adverse effects of TME in the Dutch TME trial reported both urinary incontinence and faecal incontinence developing in almost 40% of patients[58], while sexual dysfunction occurs in more than half of patients[59] after TME only. This study demonstrated that TME itself, causing nerve damage and anatomical changes, seems to be the main cause of functional morbidity after rectal cancer treatment. Regarding short-term toxicity during SCRT, negligible additional toxicity was reported in the Dutch TME trial during the 5 days of SCRT[60]. The German Rectal Cancer Study Group trial[30] demonstrated that neoadjuvant CRT with 5-FU in patients with LARC resulted in fewer short- and long-term adverse effects than after postoperative CRT. With regards to long-term adverse effects, no difference was found between CRT and SCRT in the Australian study randomizing between SCRT followed by direct TME and CRT followed by delayed TME[32]. However, in the Dutch TME trial, at 5 years after treatment, faecal incontinence was reported by 62% of patients after SCRT and TME versus 39% after TME only[61]. Sexual dysfunction occurred more frequently in the radiotherapy arm[59]. In conclusion, additional radiotherapy increases local control but adds adverse effects in comparison to TME alone.

As the age of the population increases the treatment of the elderly plays an increasingly important role. Patient tailored treatment is needed in this fragile patient category known to have higher post-operative six-month mortality rates[62]. Of note, the mortality as a consequence of anastomotic leakage is much higher than in younger patients, while the leakage rate is equal. Rutten *et al*[62] went on to contemplate that treatments that keep extent of surgery and associated morbidity to a minimum and optimize the use of radiotherapy might be more suitable for elderly patients with diminished physiological reserves and co-morbidity.

OPTIMIZING TARGET VOLUMES IN RADIOTHERAPY

One of the principle goals in the radiotherapeutic field includes maximizing efficacy and minimizing damage of healthy tissue with subsequent toxicity. To achieve this, great accuracy and a well-defined target volume is required. Three different target volumes are important in radiotherapy, the gross tumour volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV). The GTV in rectal cancer is defined as the actual visible primary tumour and any involved lymph nodes. The

CTV is the GTV plus the volume that is suspected to contain microscopic tumour deposits. However, in radiotherapy more uncertainties prevail and include day to day variation (of the CTV) within a patient due to organ motion and with respect to the setup on the treatment machine[63]. These uncertainties are taken into account by expanding the CTV with a safety margin to a PTV[64]. The larger the PTV margin, the more certain it is that the CTV will receive the prescribed dose; however, the more healthy tissue will be included in the field of radiation, resulting in unnecessary toxicity.

As microscopic tumour deposits are undetectable on imaging, anatomical guidelines for CTV definitions have been developed[65] based on (non-irradiated) patterns of local recurrence. A recent 3D analysis of local recurrences of the Dutch TME trial reported very few recurrences above the S2-S3 interface leading to lowering of the cranial border of the CTV in patients with expected pN0 and CRM negative disease[66]. The CTV is typically defined by manual delineation on a planning CT-scan and presently encompasses the (meso)rectum and the lymph nodes of the presacral, obturator and internal iliac region. Cranially, the (meso)rectum CTV is bordered by the sigmoid curve while the caudal border depends on the planned operation. In case of an APR the perineum is included, while for all other tumours the entire mesorectum is delineated down to at least 4 cm under the tumour. For the coming years the challenge will be to describe the complete CTV more extensively and finally reach consensus on CTV delineation.

The most important organs at risk during RT for rectal cancer are the small bowel, followed by the sphincter complex. Over the years, developments in RT delivery and planning have decreased irradiation to the small bowel by increasing the number of angles, size and different shapes of the beam. Conventional RT has been replaced by 3- or 4- field techniques to spare healthy tissue without compromising treatment of the target volume. With the introduction of the multi-leaf collimator the shape of each beam can be adapted to the actual shape of the PTV, resulting in conformal RT. Nowadays, we have the ability to deliver the RT dose using intensity modulated radiotherapy where, for instance, 7 beams from different angles can be subdivided into segments, with variable intensity. However, as a result, dose fall-off becomes steeper and therefore margins need to be accurate and variations accounted for, to avoid under dosage. To assure correct patient position during RT a low dose CT scan can be made during treatment (so called cone beam CT). Still, more insight in organ motion is needed to guarantee adequate treatment delivery.

THE INCREASING ROLE OF THE PATHOLOGIST

Pathology plays an important role in rectal cancer staging and prediction of prognosis. Rectal cancer is staged according to the Tumour Node Metastases (TNM) classification[9]. As illustrated in Figure 2, a T1 tumour stays confined to the (sub)mucosa, a T2 invades the muscularis propria, and a T3 invades further through the muscular layer into the mesorectal fat tissue, while a T4 tumour grows through the serosa or invades surrounding organs. The nodal stage includes N0, meaning lymph node negative disease; N1 includes metastases in 1-3 regional lymph nodes; while N2 includes more than 3 positive regional lymph nodes. The presence of distant (systemic, peritoneal or lymph node) metastases is

shown by the M, whereby M1 entails distant metastases. The TNM stage is defined as pTNM when based on pathology and as cTNM when based on (preoperative) clinical findings. When preoperative therapy may have induced a response (for instance after chemoradiotherapy) it becomes ypTNM.

Subsequent versions of the TNM have been introduced over the years, dividing a category into subcategories, in an attempt to further refine prognosis. Refinements in the TNM classification every 5–7 years, however, mean that comparisons across studies and clinical trials that have been performed using earlier editions of the TNM system are no longer possible without first revising the pathology using the new version. Therefore, but also due to its higher reproducibility, Dutch national guidelines[1] state that the 5th TNM version[9] (instead of the recently introduced 7th) should be used for the staging of rectal cancer.

In the last decades, the role of the pathologist in the treatment of rectal cancer has evolved tremendously. The pathologist has become a key player in assessing quality of surgery and giving feedback to the multidisciplinary team. The improvements in preoperative staging and surgical technique are the result of an increased understanding of the microscopic locoregional spread of rectal cancer in the mesorectum. In 1943, Dukes[67] presented his presidential address on pathological aspects of rectal cancer demonstrating the prognostic importance of tumour characteristics like depth of invasion, location, venous invasion, lymphatic spread and tumour-free margins. Forty years later, extensive pathologic research by Quirke[68] has revealed the importance of the lateral or circumferential resection margin (CRM) as a prognostic factor for local recurrence. Patients with tumour in the inked CRM but also those with tumour cells approaching the CRM within 1 mm were at risk and developed a LR in 80%. A positive CRM, as shown in Figure 4, is defined as primary tumour or a positive lymph node found ≤ 1 mm from the CRM. These results confirmed the findings by Heald[69] implementing TME in the same period and led to fewer positive margins and less residual disease. In a review, Nagtegaal *et al*[70] demonstrated that after the introduction of TME, and even more so after the introduction of neoadjuvant therapy, CRM remains a powerful prognosticator, predicting LR, distant metastases and overall survival. In LARC patients undergoing CRT, local recurrence occurs in only 8% of the patients with a negative CRM compared with 43% in case of CRM involvement[71].

After the introduction of neoadjuvant (C)RT histological alterations occur of which the prognostic value is yet to be defined[73]. In up to 30% of patients a pathological complete response (pCR) is observed after CRT, with no viable primary tumour cells in the specimen. The pCR rate may also vary due to differences in the pathology protocol used to exclude residual disease. Incompletely understood entities include the heterogeneous response observed after CRT, the meaning of the formation of fibrosis, residual tumour deposits and tumours that are replaced by acellular mucin lakes. The histopathological regression of tumour to the CRT is assessed by semi-quantitatively scoring the relative proportion of residual tumour to stromal fibrosis (tumour regression grade[74] or TRG), and has been correlated with outcome. Since reproducibility of several commonly used five tiered tumour regression grading systems is notoriously poor, no system has gained acceptance in practice. More subgroups, in poor responders in particular, decrease reproducibility[71].

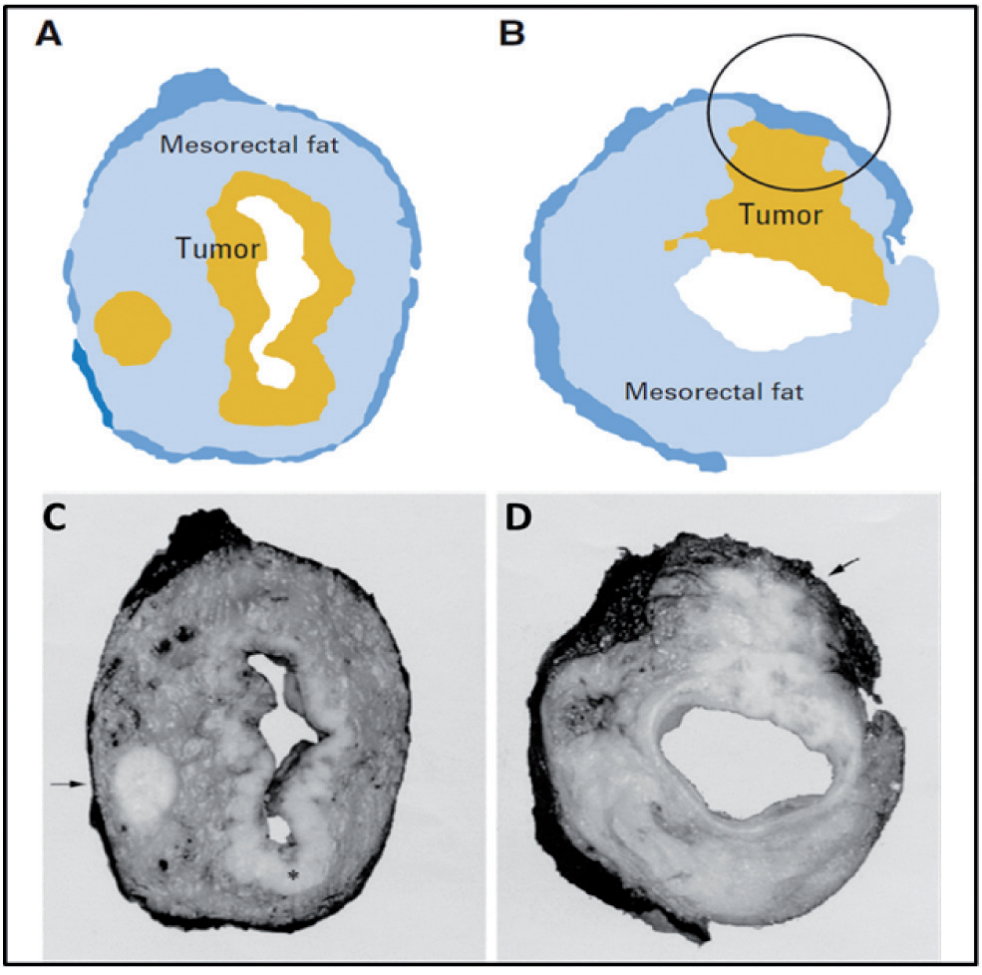

Figure 4: Schematic representation of the macroscopic histopathological view of the circumferential resection margin in resection specimens. In A and C a positive lymph node is situated close to the CRM, as indicated by the arrow. In B and D the primary tumour invades into the perirectal fat tissue close to the CRM, as indicated by the arrow. Reprinted with permission © 2013 American Society of Clinical Oncology[70] and American Journal of Surgical Pathology[72]. All rights reserved.

DISTANT METASTASES IN RECTAL CANCER

Following the improvements in local control, distant metastases occurring in up to 30% of patients remain a problem and govern outcome in rectal cancer[26;75]. Adjuvant systemic chemotherapy (CT) seems to be the obvious means of attacking micro-metastases to prevent these metastases, but evidence for its efficacy in rectal cancer is poor and much less than in colon cancer[76-78]. Furthermore, no significant gain in survival was observed when adding CT to RT followed by surgery in rectal cancer patients[4;29]. In the QUASAR study, conducted in predominantly low-risk colorectal cancer patients in

Western countries in the pre-neoadjuvant therapy era, an improvement in survival was observed[79], while in another study in the same period benefit was found in colonic cancer but not for rectal cancer[80]. A recent Cochrane meta-analysis showed a reduction of 17% in the risk of death after adjuvant CT in comparison to surgery alone, once again, in the pre-neoadjuvant therapy era[81]. In contrast, an exploratory analysis of an EORTC trial suggested that for patients responding to neoadjuvant treatment with a ypT0-2 result, adjuvant CT improved survival[82] while those not responding to CRT also do not benefit from adjuvant CT. A recent European Consensus Conference failed to reach consensus regarding the benefit of postoperative CT after CRT, because of insufficient evidence[83]. In the Dutch rectal cancer guidelines, adjuvant chemotherapy is administered only in trial setting. Results from the recently closed Dutch randomized SCRIPT trial which addresses this question are awaited. In other countries, national guidelines support adjuvant CT as standard of care. The benefit in those with a complete response or those with a ypN0 stage has, however, been questioned[84].

Peritoneal carcinomatosis (PC) is another location for distant metastases present in approximately 10% of patients with colorectal cancer at the time of diagnosis and in about 25% of patients with recurrent disease. PC seems to behave differently than the systemic metastases to the liver and lungs. It has been suggested that if distant metastases are limited to the peritoneal cavity, PC should be regarded as locoregional disease progression rather than systemic progression. Prolonged survival using a new treatment technique, cytoreduction followed by hyperthermic intra-peritoneal chemotherapy (HIPEC) has been reported[85]. The concept entails cytoreductive surgery whereby all macroscopic disease is removed by organ resection or peritoneal stripping. The intra-operative intra-peritoneal lavage with chemotherapy then eradicates microscopic disease, while hyperthermia improves peritoneal permeability and cytotoxicity. Verwaal *et al*[86] published the only randomized controlled trial to date, demonstrating improved survival after cytoreduction followed by HIPEC compared to systemic treatment in patients with PC. As a result of the randomized trial, cytoreduction followed by HIPEC has been introduced in the Netherlands and since then more than 1000 procedures have been performed over 5 institutes.

Cytoreduction is attempted only in those in which a complete cytoreduction is probable, as otherwise patients do not benefit from the treatment. As present day imaging cannot detect PC accurately, exploration of the abdomen is the only way to gain information on extent of disease. Different scoring systems are in use to score extent of disease upon opening the abdomen but evidence is lacking to support one in particular.

QUALITY ASSURANCE IN RECTAL CANCER

From the above it is clear that the treatment of rectal cancer has evolved from a mono-disciplinary surgical approach to multidisciplinary team work. Variability in care inevitably causes variability in quality of care. Improving surgical quality therefore also implies reducing variability among surgeons. Total mesorectal excision is a technically demanding operation and quality is surgeon-dependent with regards to volume and case-mix[87]. With regards to daily practice, the multimodality character and

different treatment approaches have made the treatment of rectal cancer complex for health care professionals. An optimal patient-tailored decision-making process requires adequate interdisciplinary communication and coordination. Burton *et al* confirmed this hypothesis, demonstrating that multidisciplinary team discussion and implementation of a MRI-guided preoperative treatment strategy resulted in significantly reduced positive CRM rates in rectal cancer patients[3]. Evidence based rectal cancer treatment guidelines[1] for the Netherlands were introduced in 2004 and recommend that all patients be discussed by a MDT, irrespective of tumour stage or treatment plan. At the MDT meeting, patients are stratified according to risk of a positive CRM, and subsequent local recurrence, and treated accordingly. Patients with a mobile, resectable tumour (cT2-3N0-1) undergo SCRT followed directly by TME while those with LARC undergo neoadjuvant CRT followed by TME 6-8 weeks later. Possible benefits of a more standardized approach to preoperative and histopathological staging are that certain parameters for quality assurance and possibilities for direct feedback to the MDT arise.

With regards to quality assurance, the first nationwide initiative to improve quality in rectal cancer started in 1993 in Norway with the Norwegian Rectal Cancer Project. Centralized treatment was implemented "top-down", TME was taught to participating surgeons and the national cancer registry collected information, thereby facilitating comparisons over the different periods. All participating institutions received feedback on their own results, benchmarking with the national average. More than 99% of patients operated for rectal cancer were included. After 4 years the results of this audit were remarkable: the proportion of TME surgery rose from 78% to 92% and the local recurrence rate dropped from 28% to 7%[88]. As a consequence, the concept of a surgical audit was established and in the meantime several European countries have embarked on a surgical audit. In 2009 the Dutch Surgical Colorectal Audit (DSCA) was initiated by the cancer care providers themselves to maximize transparency in quality of care from a "bottom up" perspective. First publications already show an increase in quality of care for these patients[89]. In addition, collaboration between different modalities has led to the publication of the SONCOS document in 2012, containing minimal requirements that need to be met by different departments of hospitals aiming to provide cancer care. Amongst others, an active MDT is required, modern imaging tools must be implemented, an annual volume of 20 TME's need to be performed and LARC has been centralized. Under supervision of the government health board, insurance companies determine financial compensations to be awarded to the hospitals on the basis of these quality care indicators.

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OUTLINE OF THE THESIS

Remaining questions and current goals in the treatment of rectal cancer include optimizing staging accuracy, establishing the optimal neoadjuvant strategy to be implemented in the different stages of rectal cancer and possibly leading to the evidence-based introduction of organ sparing and non-operative strategies in selected patients. Furthermore, adverse effects of new multi-modality treatments need to be investigated to properly inform patients. Correlating histopathological response to outcome will provide information on efficacy of new neoadjuvant therapies, factors governing distant metastases and potential consequences of scaling down treatment approaches to avoid surgery. The aim of this thesis, addressing the different modalities, was to evaluate these aspects concerning the multidisciplinary treatment of rectal cancer in general, with the focus on patients with locally advanced rectal cancer in particular.

As the treatment of rectal cancer has evolved it is important to introduce these improvements in all hospitals treating rectal cancer thereby maximizing patient benefit. In **Chapter 2** an overview of the adherence to treatment guidelines for rectal cancer is presented in the form of a population-based study with the aim of improving the exposure of all patients to modern rectal cancer treatment. Particular attention was paid to present staging accuracy and the additional value of the discussion of patients in a multidisciplinary team. The **3rd Chapter** captures developments in the delivery of target volumes in radiotherapy and reports results from a prospective repeat-CT study to describe full 3D shape variation for the entire clinical target volume for rectal cancer during short-course radiotherapy and chemoradiotherapy. This chapter also describes and validates a pragmatic approach to translate clinical target volume shape variation into a planning target volume margin with the aim to decrease radiation dose to surrounding healthy tissues. In **Chapter 4** acute toxicity and surgical complications were evaluated in patients with locally advanced rectal cancer. Results are presented from a relatively large series of patients treated uniformly with neoadjuvant chemoradiotherapy with capecitabine followed by total mesorectal excision 6-8 weeks later. **Chapter 5** reports the results after central revision of the histopathology of the patients discussed in chapter 4. Objective of this study was to evaluate which factors determine outcome, focusing on the contribution of histopathological response after chemoradiotherapy and the possible consequences for a “wait and see” policy. The **6th Chapter** describes demarcation of the rectal tumour with endoclips placed around the tumour during sigmoidoscopy before radiotherapy treatment. Results are shown of our evaluation of long-term attachment of two different endoclips in the human gastrointestinal tract. **Chapter 7** concerns patients with peritoneal carcinomatosis of colorectal origin who underwent cytoreduction and HIPEC. In this study three different scorings systems used to quantify extent of tumour load at laparotomy were compared. In **Chapters 8 - 10** the thesis is concluded with a general discussion and future perspectives, bibliography followed by a bilingual summary.

CHAPTER 2

Multidisciplinary discussion and management of rectal cancer: a population-based study

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ABSTRACT

BACKGROUND

The purpose of the present study was to evaluate the value of discussing rectal cancer patients in a multidisciplinary team (MDT).

METHODS

All treated rectal cancer patients (>T1M0) diagnosed in 2006–2008 were included. According to the national guidelines, neoadjuvant (chemo)radiotherapy should be given to all rectal cancer patients. Patients were scored as ''discussed'' (MDT+) only if documented proof was available. The primary endpoint was the number of positive circumferential resection margins (CRM ≤1 mm).

RESULTS

Of the 275 patients included, 210 were analysed (exclusions: (recto)sigmoid tumour, acute laparotomy, and inoperability). Neoadjuvant treatment was applied in 174 (83%) patients and followed by total mesorectal excision in 171 (81%) patients. Patients considered not to require downstaging, received short-course radiotherapy (SCRT) (n = 116) or no radiotherapy (no RT) (n = 36), whereas 58 more advanced patients received chemoradiotherapy (CRT). The MDT discussion took place in 116 cases (55%). In the MDT+ group an MRI was used more often (p = 0.001) and TNM staging was more complete (p<0.001). The proportion of patients with advanced disease was higher in the MDT+ group (88% ≥T3/N+ versus 68%; p = 0.001). The overall CRM+ rate was 13% and did not differ between the MDT+ and the MDT– group (p = 0.392). In patients receiving SCRT or no RT, the CRM+ rate was 10%, whereas the rate was 20% for patients receiving CRT.

CONCLUSION

Although no difference in CRM+ rate was found for those patients who were discussed and those who were not, our results demonstrate room for improvement, especially in the selection of patients for SCRT or no RT. We advocate standardized documentation of treatment decisions and pathology reports.

INTRODUCTION

Over the last 10-15 years, the treatment of rectal cancer has evolved tremendously. Results of randomized controlled trials[20;30;90] have led to the introduction of "total mesorectal excision" (TME)[69] and preoperative (chemo)radiotherapy in Western Europe. Further research has established the role of the pathologist and radiologist in optimizing the multidisciplinary treatment of rectal cancer. Identification of tumour ≤ 1 mm from the circumferential resection margin (CRM+) has proven to be a strong predictor of local recurrence, distant metastases and survival, resulting in a new surrogate endpoint of rectal cancer treatment[70;91-93]. Meanwhile, two radiological studies[11;94] demonstrated that MRI can accurately predict involvement of this surgical CRM, thereby shifting the importance of an accurate T-stage on MRI to the more clinically appealing mesorectal fascia (MRF) at risk for a positive CRM after TME.

With regards to daily practice, the multimodality character and different treatment approaches have made the treatment of rectal cancer complex for health care professionals. An optimal patient-tailored decision-making process requires adequate interdisciplinary communication and coordination. Burton *et al* have shown that a MRI directed multidisciplinary team (MDT) discussion of rectal cancer patients with implementation of a preoperative stratification significantly reduced the CRM+ rate[3]. In certain patients groups, MDT discussion is increasingly becoming standard of care, but evidence of its direct effect on the quality of cancer care remains limited[95]. Rectal cancer treatment guidelines for the Netherlands were introduced in 2004 and recommend that all patients be discussed by a MDT, irrespective of tumour stage or treatment plan. At the MDT meeting, patients are stratified according to risk of a positive CRM, and subsequent local recurrence, and treated accordingly. Possible benefits of a more standardized approach to preoperative and histopathological staging are that certain parameters for quality assurance and possibilities for direct feedback to the MDT arise. For instance, patients receiving short-course radiotherapy (SCRT) or TME only should all have a negative CRM after TME, as otherwise chemoradiotherapy (CRT) was the preferred preoperative treatment to induce preoperative downstaging.

We studied surgical outcome after the introduction of TME with the administration of (chemo) radiotherapy in selected cases of rectal cancer in the greater Amsterdam region. The aim of this population-based study was to evaluate the additional value of discussing rectal cancer patients in a MDT, with the occurrence of a positive CRM as endpoint. Additional aims were to audit preoperative and histopathological staging and the implementation of preoperative risk stratification according to national guidelines.

PATIENTS AND METHODS

PATIENTS

All patients diagnosed with cT2-4, N0-2 rectal cancer (TNM, 5th edition[9]) in one of six referring hospitals and one cancer referral centre in the greater Amsterdam region, between January 2006 and January 2008, were included in the study. Exclusion criteria included patients with low risk cancer (cT1N0) receiving local excision only, previous invasive cancers, a tumour located above the peritoneal deflection or more than 15 cm from the anal verge, or patients with metastasized disease.

DATA COLLECTION

The Comprehensive Cancer Centre Amsterdam (CCCA) is an independent regional, population-based cancer registry with complete coverage of a population of approximately 3 million inhabitants. Following histopathological diagnosis, cancer patients are identified from the nationwide pathology registry (PALGA) and prospectively entered into the registry. This pathology registry also assures complete coverage of all patients diagnose in the region enabling a true population based study. Registration clerks routinely extract data on tumour stage, treatment and follow-up from hospital and outpatient records. Additional information, not routinely collected, was collected retrospectively by the registration clerks of the CCCA or by one of the authors (HAMS and EGP) and included type of imaging for preoperative staging, discussion by a MDT, treatment decisions and treatment outcome.

MDT

In the regional referral network of the cancer institute, patients are discussed in a multidisciplinary oncology meeting at the referring hospital. During an MDT discussion patient history, clinical and psychological condition, comorbidity, modes of work-up, clinical staging and optimal treatment strategies are discussed. The multidisciplinary team members present include a consulting oncologic surgeon, a radiation oncologist and a medical oncologist (all from the cancer institute), the treating specialists (surgical oncologist, medical oncologist) as well as a radiologist, a pathologist and a specialized nurse (nurse practioner or case manager). If the MDT at the referring hospital decides to treat the patient with neoadjuvant radiotherapy, the patient is referred to the cancer institute. In case of doubt, when the optimal treatment approach is queried by the radiation oncologist at the cancer institute, or when a locally advanced tumour is suspected, the patient is also discussed in the cancer institute's specialized gastrointestinal cancer MDT.

Patients were scored as "discussed" (MDT+) only if documented proof was available that the patient had been discussed preoperatively at a MDT meeting, either in a referring institute or in the cancer institute.

TREATMENT

In the Netherlands, patients are stratified into three risk groups, each with a different treatment approach based on the risk of a positive CRM and subsequent local recurrence. Low-risk patients, defined as those with superficial tumours (T1N0) where treatment with local excision suffices, were excluded from the study. The intermediate risk group consists of patients with mobile resectable tumours (T2 and small T3, N0-1), suitable for treatment with preoperative 5x5 Gy radiotherapy (short-course radiotherapy, SCRT) followed directly by TME. In patients with small proximal tumours without clinical node metastasis, where the additional value of radiotherapy is under debate, preoperative SCRT may be withheld after discussion in a MDT. The high-risk group includes patients with locally advanced tumours, where the MRF and consequent surgical CRM is threatened or involved, or where extensive lymph node involvement is expected. In this group, the treatment of choice consists of preoperative downstaging with long-course radiotherapy (25x2 Gy) in combination with fluoropyrimidine-based chemotherapy[4;29;30;96], followed by TME 6-8 weeks later. Standard chemotherapy in the study period was capecitabine, 825mg/m2, bid on days 1-33. In three patients, bevacizumab (5mg/kg i.v. on days -14, 1, 15 and 29) was added in trial setting. Four patients received 50 Gy only as chemotherapy was contraindicated.

PATHOLOGY

An involved CRM (CRM+) was defined as tumour or an involved lymph node ≤1 mm from the CRM. If the CRM was not mentioned in the report (n=81), additional investigation of the CRM was performed by a pathologist (MLV).

STATISTICAL ANALYSIS

Data were entered into a database and analysed using the Statistical Package for the Social Sciences (version 15.0 for Windows; SPSS, Chicago, Illinois, USA). To determine significance in differences between groups of patients, chi-square tests were used for categorical variables unless stated otherwise, while the t-test and Mann-Whitney test were used for continuous variables. A p-value of < 0.05 (two-sided) was regarded statistically significant.

RESULTS

Initially, 275 patients with intermediate or high-risk rectal cancer were identified. Inoperable patients (n=24), patients undergoing non-elective surgery (n=1) or those with a (recto)sigmoid tumour (n=40) were excluded, leaving 210 patients suitable for analysis. Fifty-five per cent (116/210) of all patients were discussed by a MDT. In Table 1, baseline patient and treatment characteristics are shown for all patients and also for MDT+ and MDT- groups. Of the discussed patients, 50% were discussed at the referring hospital only, 20% were discussed both at the referring hospital and at the cancer institute, while 30% were discussed at the cancer institute only.

Table 1: Patient and Treatment characteristics according to discussion by a MDT

		Total		MDT +		MDT –		
		n=	% [a]	n=	%[a]	n=	%[a]	p-value
Total patients		210	100	116	55[b]	94	45[b]	0.147[c]
Sex	Male	122	58	63	54	59	63	0.217
	Female	88	42	53	46	35	37	
Age	Median	70		69		70		0.312
	Range	37-89		37-87		41-89		
Tumour location	0-5cm	75	36	52	45	23	24	0.002
	6-10	89	42	46	40	43	46	
	>10	45	21	17	15	28	30	
	Unknown	1	1	1	1	0	0	
MRI	Yes	175	83	106	91	69	73	0.001
	No	35	17	10	9	25	27	
Clinical tumour stage (cT)	1	6	3	2	2	4	4	0.001[d]
	2	47	22	20	17	27	29	
	3	103	49	67	58	36	38	
	4	30	14	25	22	5	5	
	Unknown	24	11	2	2	22	23	
Clinical node stage (cN)	0	108	51	55	47	53	56	0.014[d]
	1	69	33	40	34	29	31	
	2	17	8	15	13	2	2	
	Unknown	16	8	6	5	10	11	
Advanced stage (≥T3 or N+) n=198	Yes	149	81	99	88	50	68	0.001
	No	36	20	13	12	23	32	
Type of preoperative treatment	None	36	17	7	6	29	31	<0.001[e]
	SCRT	116	55	61	53	55	59	
	CRT	58	27	48	41	10	11	
Type of surgery	LAR	115	55	48	41	67	71	<0.001[f]
	Hartmann	28	13	20	17	8	9	
	APR	64	31	46	40	18	19	
	No surgery	3	1	2	2	1	1	
Histopathological tumour stage (pT) n=207	0	9	4	8	7	1	1	0.262[d]
	1	20	10	11	10	9	10	
	2	68	32	35	31	33	35	
	3	102	49	56	49	46	49	
	4	8	4	4	4	4	4	
Histopathological nodal stage (pN) n=207	0			73	64	57	61	0.437[b]
	1			26	23	24	26	
	2			15	13	11	12	
	Unknown			0	0	1	1	

Abbreviations: SCRT: short-course radiotherapy. CRT: chemoradiotherapy. LAR: low anterior resection. APR: abdominoperineal resection. Pt: patients. a) Percentages are column percentages unless stated

otherwise and are rounded off. b) Percentage is of the total number of patients. c) Binomial test. d) Linear-by-linear association. e) (Chemo) radiotherapy versus no radiotherapy. f) APR versus sphincter sparing surgery.

STAGING

Of the 210 patients, 178 (85%) had a clinical TNM stage, including both T and N-stage, reported. In the MDT+ group, staging was more complete (94% versus 73%, p<0.001) while a MRI was also performed more often (p=0.001). In addition, the proportion of patients with advanced disease (≥T3 and/or N+) was higher (p=0.001) in the MDT+ group. Correlation of the clinical and pathological T and N stages of the subgroup of patients receiving SCRT or TME only (to exclude downstaging effects of CRT) revealed a staging accuracy for T-stage of 57% (Table 2) and N-stage of 63%. In Table 2 only patients with complete cT and pT were included. No significant difference in tumour or nodal staging accuracy (understaging, accurate, overstaging) was found between MDT+ and MDT- groups (p= 0.139 and 0.902).

TREATMENT

Preoperative (chemo)radiotherapy was applied in 174 (83%) patients. Three patients did not proceed to surgery due to death during CRT, poor performance status and local progression, respectively. Thirty-six patients underwent TME only. Patients receiving preoperative (chemo)radiotherapy were discussed more often in a MDT than those undergoing TME only (63% versus 19%, p<0.001). Furthermore, patients with distal tumours (≤5 cm from the anal verge) were more likely to be discussed in a MDT than those with more proximal (6-15 cm) tumours (69% versus 47% MDT+, p=0.002).

OUTCOME

The CRM was initially reported in 126 (61%) and additionally measured in 71 (34%) of the 207 resected patients, while in 10 patients the CRM remained unknown. In total, in 24 patients a positive CRM was documented after resection, while in one patient the tumour was irresectable after CRT, resulting in an overall CRM+ rate of 13% (25/198). An APR was not associated with significantly more CRM+ resections (18% versus 10% after sphincter saving resections, p=0.093). Increasing pathological T- and N- stage were both associated with increasing CRM+ rates (p=<0.001 and p=0.001, respectively).

The flow diagram in Figure 1 illustrates outcome after different treatment strategies. The CRM+ rate for intermediate risk patients (i.e. receiving SCRT or no radiotherapy) was 10% (14/143) while it was 20% (11/55) after CRT (including one irresectable patient). Furthermore, in the intermediate risk subgroup, distal tumours were associated with more CRM+ resections (8/38 CRM+, p=0.011) compared to those located 6-15 cm from the anal verge (6/105 CRM+).

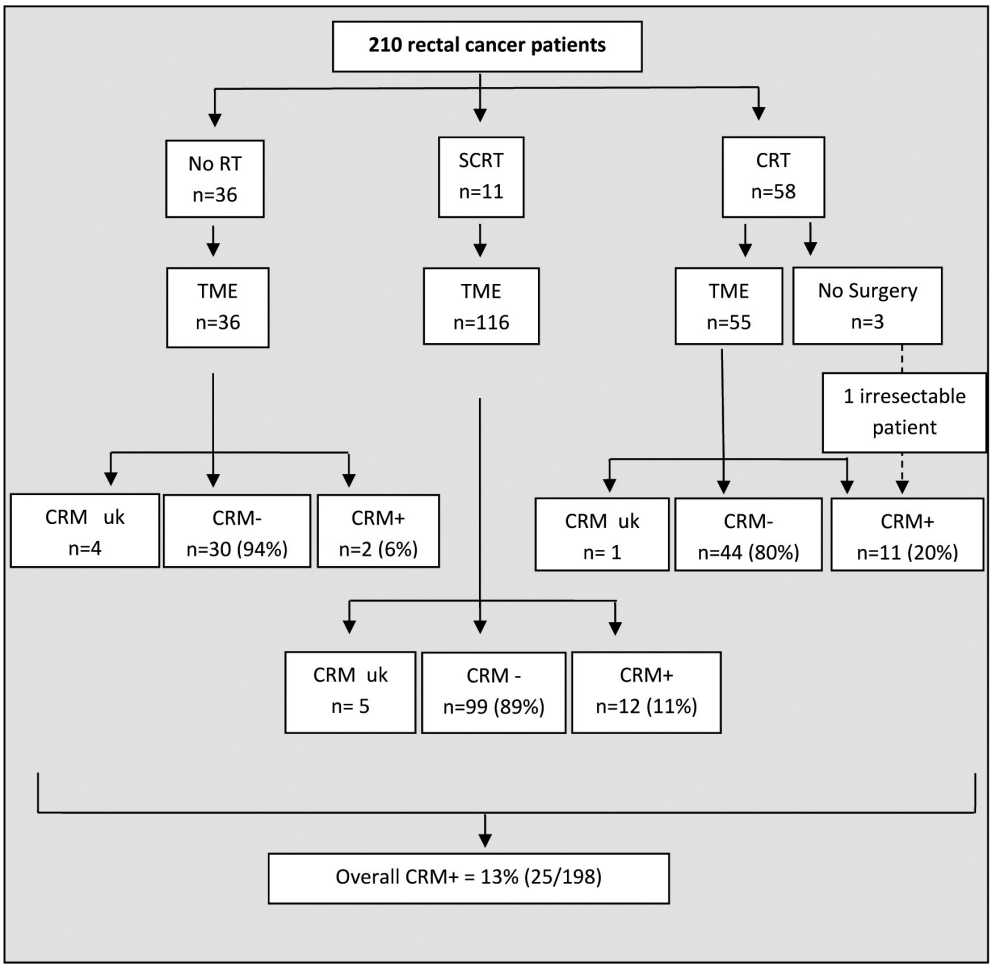

Figure 1: Flow diagram of treatment and CRM+ rate

Table 3 shows CRM involvement according to MDT discussion. The overall CRM+ rate did not differ significantly between the MDT+ (14%, 16/111) and the MDT- (10%, 9/87) group (p=0.392), even when patients with a positive CRM determined by an involved node were excluded from the comparison (p=0.198). When analysing the subgroup of intermediate risk patients (receiving SCRT or no RT) only, the CRM+ rate remained similar (12% versus 8%, respectively; p=0.385). The root-cause analysis in Table 4 describes the characteristics and treatment of those patients with a CRM+ outcome after TME only or SCRT. Of these 14 patients with a positive CRM, not treated with CRT, discussion in a MDT could not prevent the positive CRM in eight patients, while six patients were not discussed by a MDT. Strikingly, in non-discussed patients with a positive CRM 3 patients had a pathological T4 tumour that was not recognized during preoperative staging.

Table 2: Correlation of the clinical and pathological T stages of the subgroup of patients not receiving CRT.

		pT				Total
		1	2	3	4	
cT	1	3	3	0	0	6
	2	10	22	10	1	43
	3	3	22	45	2	72
	4	0	1	2	1	4
Total		16	48	57	4	125

Table 3: shows CRM involvement according to MDT discussion

	MDT + (%) n=114				MDT- (%) n=94				Total
Preoperative treatment	CRM >1mm	Primary tumour ≤1mm	Positive node ≤1mm	uk	CRM >1mm	Primary tumour ≤1mm	Positive node ≤1mm	uk	
None	6 (100)	0	0	1	24 (92)	1 (4)	1 (4)	3	36
SCRT	52 (87)	7 (12)	1 (2)	1	47 (92)	3 (6)	1 (2)	4	116
CRT	37 (82)	7 (16)	1 (2)	1	7 (70)	2* (20)	1 (10)	0	56
Total	95 (86)	14 (13)	2 (2)	3	78 (90)	6 (7)	3 (3)	7	208*

** Including 1 irresectable tumour. Abbreviations: MDT +: Discussed by a multidisciplinary team. MDT-: Not discussed. CRM: circumferential resection margin. CRT: chemoradiotherapy. SCRT: short-course radiotherapy. uk: unknown*

DISCUSSION

This population based study represents daily practice in the Netherlands in the era following the TME trial. Only half of the patients diagnosed with rectal cancer in our region are discussed by a MDT. As predominantly advanced patients were selected for discussion, this may have influenced the study outcome whereby no significant benefit was found for MDT discussion on the CRM+ rate. We found an overall CRM+ rate of 13%, while for the subgroup of patients in which preoperative downstaging was not deemed necessary, the rate was 10%. Documenting the CRM in the pathology report has not yet become standard of care, as initially it was documented in only 61% of patients.

Table 4: CRM positive patients: a root-cause analysis.

Pt nr	Tumour height (cm)	MDT +/- and location	MRI	Preoperative therapy	Operative procedure	CRM (mm)	Tumour or node at CRM	TN stage
1	0-5	-	No	None	Hartmann	0	Tumour	cT4Nx, pT4N0
2	0-5	-	Yes	SCRT	LAR	0	Lymph node	cT3N1, pT3N1
3	0-5	-	Yes	SCRT	LAR	≤1	Tumour	cT3N1, pT3N0
4	0-5	Referring hospital	Yes	SCRT	Hartmann	≤1	Tumour	cT3N0, pT3N2
5	0-5	Referring hospital	Yes	SCRT	APR	≤1	Tumour	cT2N0, pT3N0
6	0-5	Referring hospital	Yes	SCRT	APR	≤1	Tumour	cT2N1, pT2N0
7	0-5	Referring hospital	Yes	SCRT	APR	0	Tumour	cT3N1, pT2N2
8	0-5	Cancer Institute	Yes	SCRT	APR	≤1	Lymph node	cT2N2, pT2N2
9	6-10	-	Yes	SCRT	LAR	0	Tumour	cT2N0, pT4N2
10	6-10	-	Yes	SCRT	APR	0	Tumour	cT3N1, pT4N0
11	6-10	Referring hospital	Yes	SCRT	LAR	0	Tumour	cT3N1, pT3N1
12	6-10	Both	Yes	SCRT	LAR	0	Tumour	cT3N0, pT3N1
13	>10	-	No	None	LAR	≤1	Lymph node	cTxN0, pT3N1
14	>10	Cancer Institute	Yes	SCRT	Hartmann	≤1	Tumour	cT3N0, pT3N1

No information on the completeness of the surgical specimen was available. Abbreviations: MDT: multidisciplinary team, CRM: circumferential resection margin, CRT: chemoradiotherapy, SCRT: short-course radiotherapy, APR: abdominoperineal resection, LAR: low anterior resection.

CRM + RATES IN THE LITERATURE

In the TME trial, patients with resectable rectal cancer were randomized between TME alone and SCRT followed by TME within 10 days. In this quality controlled study undertaken in the era preceding the use of MRI, the reported CRM+ rates after macroscopic complete resection were 18% and 16%, respectively[27]. The CRM rate of 10% in patients receiving SCRT or TME only in our study reflects progression in this field; but it also illustrates room for further improvement in patient selection, especially in patients receiving SCRT (11% CRM+). In the MRC CR07 study, a study comparable to the TME trial, the CRM+ rates were 10% of those undergoing a macroscopic complete resection in the SCRT arm and 12% in the TME alone arm[90]. During this study period the MRI was being introduced as selection tool, with 41% of patients staged with MRI, indicating the advantages of MRI on patient selection.

EFFECT OF THE MDT DISCUSSION

Dutch rectal cancer treatment guidelines recommend discussing all patients in a MDT meeting. As mentioned above, our study shows that this is not yet the case in our region.

Despite the fact that recording the results of the MDT discussion is mandatory in the Netherlands, it is possible that we underestimated the number of patients discussed due to a lack of documentation. The use of a pro forma for all patients would facilitate more complete documentation of the discussion or the reason why a patient was not discussed. Burton[3] evaluated the effects of regional implementation of a MDT discussion and reported a CRM+ rate of 13%, which is equal to ours. In contrast to our study, they showed that discussion by a MDT was associated with a significantly lower CRM+ rate (26% versus 8%). At re-audit one year later, after introduction of compulsory MDT discussion for all rectal cancer patients, 96% were discussed and the CRM+ rate was decreased to 7% overall, which emphasizes the importance and effect of multidisciplinary interaction in their region. Due to a selection of advanced patients for discussion a true comparison between MDT+ and MDT- patients in our series is difficult, especially because advanced patients have a higher a-priori risk of a CRM+ resection, thereby undermining the value of the MDT. Although acceptable CRM+ rates were obtained with this selective discussion approach, there is room for improvement. In fact, six CRM+ patients, who were not discussed and received SCRT or no RT, might have benefitted from a discussion by a MDT. This is underscored by the fact that three of these patients had a pT4 tumour, indicating that CRT was absolutely necessary. We therefore advocate discussion of all rectal cancer patients in a MDT.

Regarding the MDT itself, eight patients discussed in a MDT received SCRT but ended up with a positive CRM, indicating that the MDT itself also needs improvement. However, another confounding factor may be the quality of the surgical specimen (Table 4).

PRE-TREATMENT STAGING

With regards to preoperative staging, T-staging accuracy with MRI was 57%, similar to that of the MERCURY group in their national MRI implementation program (53%)[97]. Inaccuracy in distinguishing T1 from a T2 (34% in our study) and T2 from a T3 (32%) reported in this study is in line with the literature and indicate that MRI does have its limits in T and N staging[11]. However, recent studies[11;94] have shown that a shift in staging has taken place from primarily an accurate T-stage on MRI to a more clinically important mesorectal fascia (MRF) at risk for a positive CRM after TME. In our study, treatment stratification was based on the risk of a positive CRM (<2 mm at risk), but exact distances to the MRF on MRI were not documented. Twelve of the 14 patients with a positive CRM after SCRT or TME only were staged with MRI, indicating that more attention is needed to accurately select patients at risk. A pro forma with standardized quantification of margins, tumour infiltration depth, and size and aspects of nodes might facilitate further optimization of staging. Furthermore, a MRI based MDT discussion will lead to a better understanding of the anatomy of the rectal tumour which is important for all specialists involved.

POST-CHEMORADIOTHERAPY RE-STAGING

In the 11 patients with a positive resection margin after CRT, a complete resection was not possible indicating that sufficient downstaging after chemoradiotherapy is not always achieved. Re-staging after chemoradiotherapy, which was not standard of care during this study period, might have optimized treatment by enabling the surgeon to plan the resection according to the (lack of) response or to even decide to delay surgery to optimise response. However, on MRI microscopic tumour deposits remain difficult to distinguish from benign desmoplastic reaction. Possibly, PET scanning will aid the identification of vital and metabolically active tumour cells in the future. Other possibilities to further decrease the CRM+ rate after CRT include centralisation of the treatment and further optimisation of the synergistic effect of chemoradiotherapy on tumour downstaging with either intensified chemoradiotherapy or tumour specific biologicals, like VEGF inhibitors. However, whether this approach will really lead to better clinical outcome remains to be seen. In the ACCORD 12 trial[33], T3-4M0 rectal cancer patients were randomised between 45 Gy RT with capecitabine or 50 Gy RT with capecitabine and oxaliplatin. A significant decrease in CRM+ resections with intensified CRT (19% versus 10%, p=0.02) was observed. Whether this was due to the increased radiotherapy dose or the addition of oxaliplatin remains speculative.

STUDY LIMITATIONS

Due to the retrospective population based nature of this study; some limitations need to be addressed. We only scored patients as MDT+ if documented proof was available that the patient had been discussed preoperatively at a MDT meeting. It is possible that the number of patients discussed in a MDT has been underreported. Exact details on and reasons underlying treatment decisions (for instance: patient unfit for chemo(radiotherapy)) were not available. Regarding patient outcome, follow-up was not long enough to be able to demonstrate the prognostic importance of a positive CRM with regards to the (local) recurrence rate or overall survival.

CONCLUSION

In conclusion, in our region MRI based preoperative stratification has led to a selective approach to MDT with 55% of patients being discussed. Even though national guidelines state that all patients should be discussed in a MDT before starting treatment this is not yet the case in clinical practice. Interestingly, even though the group of patients discussed consisted of patients with higher risk for a positive CRM due to their advanced stage of disease, this did not result in more CRM positivity in comparison to the group of patients not discussed by a MDT with predominantly less advanced disease. In this latter group one would expect less positive CRM resections. The CRM+ rate of 10% in patients not receiving CRT indicates room for improvement. The message of this study is clear; the implementation of MRI in optimizing patient selection has not yet reached its full potential. Standardized staging (MRI and histopathology) in all rectal cancer patients will lead to improvement of rectal cancer treatment and create opportunities for feedback to the MDT.

ACKNOWLEDGEMENTS

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CHAPTER 3

Repeat CT assessed CTV variation and PTV margins for short- and long-course preoperative RT of rectal cancer

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ABSTRACT

BACKGROUND

To quantify the inter-fraction shape variation of the CTV in rectal cancer patients treated with 5 x 5 (SCRT) and 25 x 2 Gy (LCRT) and derive PTV margins.

METHODS

Thirty-three SCRT with daily repeat CT scans and 30 LCRT patients with daily scans during the first week followed by weekly scans were included. The CTV was delineated on all scans and local shape variation was calculated with respect to the planning CT. Margin estimation was done using the local shape variation to assure 95% minimum dose for at least 90% of patients.

RESULTS

Using 482 CT scans, systematic and random CTV shape variation was heterogeneous, ranging from 0.2 cm close to bony structures up to 1.0 cm SD at the upper-anterior CTV region. A significant reduction in rectal volume during LCRT resulted in an average 0.5 cm posterior shift of the upper-anterior CTV. Required margins ranged from 0.7 cm close to bony structures up to 3.1 and 2.3 cm in the upper-anterior region for SCRT and LCRT, respectively.

CONCLUSIONS

Heterogeneous shape variation demands anisotropic PTV margins. Required margins were substantially larger in the anterior direction compared to current clinical margins. These larger margins were, however, based on strict delineated CTVs, resulting in smaller PTVs compared to current practice.

INTRODUCTION

The standard of care for early-stage and locally-advanced rectal cancer has evolved to preoperative short-course radiotherapy (RT) followed by a total mesorectal excision (TME) and long-course chemo-RT followed by a TME, respectively[24;26;90;98;99]. The side-effects of RT can be reduced by advanced treatment delivery techniques such as intensity modulated RT (IMRT)[100;101]. To assure clinical target volume (CTV) coverage with IMRT a proper planning target volume (PTV) margin should be applied accounting for all geometric uncertainties. The known dominant uncertainties in RT of rectal cancer are CTV shape- and delineation-variation with systematic and random errors up to 1 cm SD. Despite the size and impact of these uncertainties, only few publications are available describing them[102-108], with the limitation of small numbers and only a part of the CTV investigated. Furthermore, there is no recipe available to calculate the required PTV margin to account for these variations. Available margin recipes are only valid for translations of rigid CTV structures[64;109]. In clinical practice often a too small uniform 1 cm PTV margin is used, for which the radiation oncologist often delineates the CTV generously to compensate for shape variation[106].

The purpose of this study was to evaluate the shape variation of the clinical target volume in both early- and advanced-stage rectal cancer and to establish subsequent planning target volume margins. The data were gathered in a prospective repeat CT (rCT) study.

PATIENTS AND METHODS

PATIENTS, SCANS AND TREATMENTS

The study was initiated in the Netherlands Cancer Institute (NKI) and expanded to the Leiden University Medical Centre (LUMC). For patients with short-course RT (SCRT) of 5 x 5 Gy, daily rCT scans were acquired. For patients with long-course RT (LCRT) of 25 x 2 Gy, daily rCT scans were acquired in the first week followed by weekly scans. The study was designed to include 40 SCRT and 40 LCRT patients, 20 male and 20 female each. Previous surgery or RT in the pelvic area and supine positioning (e.g. due to stoma) were exclusion criteria.

All CT scans were acquired in prone position, on a flat table, ranging from the L2-L3 junction to below the perineum. A rotated knee support was placed under the lower legs for immobilization. When clinically feasible, intravenous contrast enhancement was used for the planning CT (pCT) only. No rectal contrast was used. All patients received instructions to empty the bladder and subsequently drink 350 ml water 1 h before the pCT and every treatment fraction. The rCT scans were planned before the treatment fraction.

STUDY DELINEATIONS

On each CT scan the following structures were delineated: bladder, rectum, and the CTV divided into the mesorectum (MesoRect), the pre-sacral lymph node region (Presacr), and the internal iliac and

obturatorial lymph node regions left and right (LN_L, LN_R) (Figure 1). The rectum was delineated from the dentate line up to the sigmoidal curve.

The MesoRect included the sphincter complex and the mesorectum with borders defined by the external sphincter, the mesorectal fascia, and had the cranial border at the same level as the rectum. In the cranial region where the mesorectal fascia could not be identified, the anterior border was delineated 0.5 cm anterior of the rectum, excluding small bowel loops.

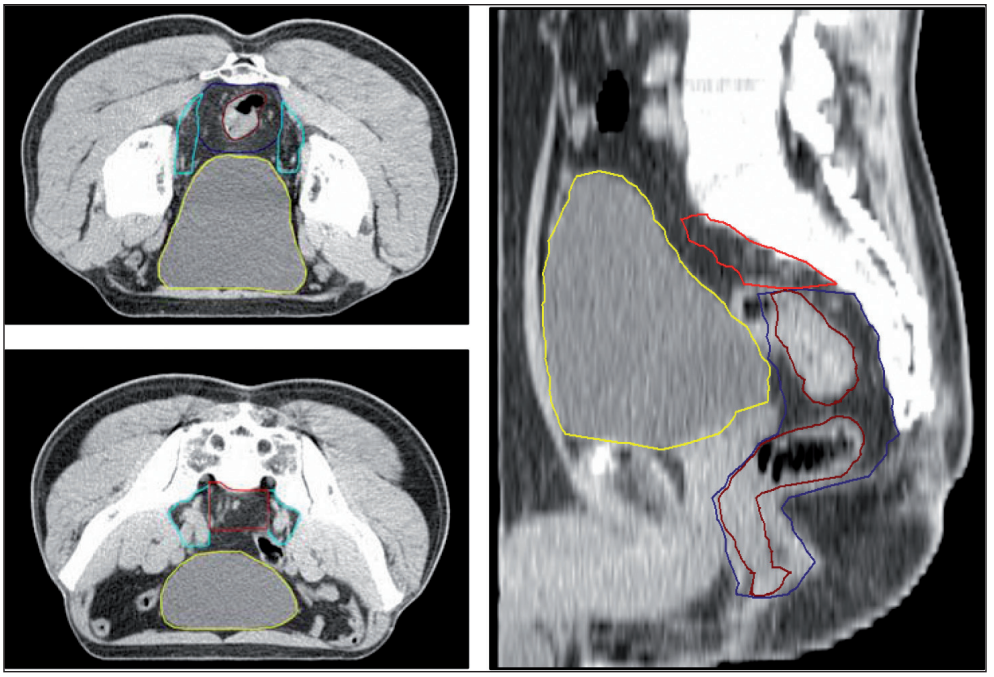

Figure 1: Example of the delineated structures on the planning CT of a male patient. On the left axial views at two different levels are shown, on the right a sagittal view. The delineated structures are the bladder, the rectum, the MesoRect including the sphincter complex, the presacral region and the lymph node regions left and right.

The LN_L and LN_R regions included the internal iliac, the lateral sacral, and the superior gluteal artery. The caudal border was where the obturator artery entered the obturator canal. The cranial border was the division of the common iliac artery in the external and internal artery. The borders were defined by the ureters anteriorly, the bones/muscles laterally, the MesoRect, seminal vesicles, uterus, neurovascular bundle medially.

The Presacr delineation connects the LN_L and LN_R from the cranial border of the MesoRect and includes the superior rectal artery. Small bowel loops were excluded from all delineations. All structure definitions were the same for SCRT and LCRT patients. The GTV was not delineated. All scans of a patient were delineated by one of five observers. The structures were first delineated on the pCT

and discussed among the observers and one radiation oncologist. The rCT scans were subsequently delineated after bony anatomy registration, using the pCT delineations as example.

SHAPE VARIATION

To compare the CTV shape variation between patients the following model was used. The MesoRect and Presacr delineation were added together (MesoPresacr) to create the central, cylinder-like, part of the CTV. The pCT MesoPresacr was sliced into 80 slices containing 100 equidistant dots per slice, with the first dot of each slice at the dorsal side. LN_L and LN_R were analysed separately, using 40 slices and 50 dots per slice, numbered starting at the mid-lateral side of the slices. The shape variation was calculated by measuring signed distances to the surfaces of the rCT CTVs perpendicular to the surface of the pCT delineation for each point. For each point the average distance and the standard deviation over the distances were calculated.

The assumption was made that the ordered points were comparable between patients, such that corresponding points could be used to calculate the local group mean (GM), systematic (∑), and random (σ) shape variation by means of the average of the averages, the SD over the averages, and the root-mean-square of the SD's, respectively. For long-course RT a normalized weighted average and SD were calculated for each patient by using a weight of 1 for the scans in the 1st week and a weight of 5 for the following scans.

MARGINS

In order to calculate the PTV margins for shape variation of the CTV, the margin recipe for rigid CTV motion of van Herk *et al*[64] was adapted. The aim was to define a margin recipe using the local group mean, systematic, and random shape variation surface maps assuring a minimum CTV dose (D_{min}) of 95% of the prescribed dose for at least 90% of the patients. In the rigid setting the PTV margin can be calculated by $m_{PTV} = \alpha * \sum + \beta * \sqrt{(\sigma^2 + \sigma_p^2)} - \beta * \sigma_p + GM$ with the SD to describe the penumbra width (σ_p) in the pelvic area taken as 0.32 cm, $\alpha = 2.5$ and $\beta = 1.64$ to meet our demands. Adaptation of the formula was needed because in a rigid setting, systematic translations always result in a movement out of the high dose region on one side, while the other side of the CTV moves within the high dose region. The effect of systematic shape variation depends on the correlation between the shape variations on different areas of the surface of the CTV[110;111]. Group mean errors are generally small and discarded, but when significant time-trends are present they can be included by simple adding to the PTV margin, taking the margin directions into account.

The effect of random errors in the setting of rigid motion or shape variation is the same, namely blurring of the dose to the CTV as a local effect. For random shape variation $1.64 * \sqrt{(\sigma^2 + 0.32^2)} - 1.64 * 0.32$ was used.

To estimate the remaining unknown factor α, the factor was varied between 2.0 and 4.0 in steps of 0.1 resulting in 21 PTVs. Each PTV was translated into an ideal dose distribution with a homogeneous dose

and a penumbra described by σ_p = 0.32 cm, resulting in a 95% isodose line at the edge of the PTV[64]. Within each dose distribution the surface dose to the CTV was accumulated by slicing each rCT CTV into 80 slices with 100 dots per slice. The dose was accumulated over the corresponding points and the D_{min} was calculated for each patient. The α-factor assuring D_{min} of 95% of the prescribed dose for 90% of the patients was finally used in the adapted margin recipe.

All calculations described above were performed perpendicular to the pCT CTV surface. Most treatment planning systems are not capable of this type of expansion and use rolling ball like algorithms. To get the rolling ball expansions the shortest distance from each PTV surface to its corresponding CTV surface was calculated locally. The median distance over corresponding points in the patient groups was taken to derive the required local rolling ball PTV margin.

Finally, sub-volumes of the CTV were visually derived based on the heterogeneity of locally defined margins. For each sub-volume a clinically applicable margin was defined in orthogonal directions. The PTVs created with these margins were dosimetrically analysed by generating ideal dose distributions and accumulation of the dose over the rCT delineations. Finally, a volumetric comparison to the actual clinical PTVs, which were based on generously delineated CTVs and a 1 cm PTV margin, was done to estimate the impact of strictly delineated CTVs plus the newly derived margins in clinical practice.

STATISTICAL ANALYSIS

For all delineations the absolute volume and the volume relative to the pCT was calculated. The relative volumes were tested to be different from 1 using a 2-sided student T-test for each rCT time point. Systematic shape variation errors between the groups were compared using a 2-sided F-test on corresponding points resulting in a p-value surface map. The GM shape errors were tested on difference from 0 using a T-test. For random errors a 2-sided T-test was used to test the means as a surrogate for the root-mean-square. In the analysis four different groups were compared, being the male and female SCRT, and the male and female LCRT patients. Significance level was set to $p < 0.05$.

RESULTS

PATIENTS

Between October 2008 and March 2011 63 patients (40 male, 23 female) were included in the study (Table 1), 60 NKI, and three LUMC. The intended 40 female patients were not reached due to more prevalence of exclusion criteria, more refusals, and less prevalence compared to male patients.

For six SCRT patients one rCT scan was missing. For LCRT one rCT scan was missing for three patients and two female patients withdrew from the study after the 1st and 2nd week, respectively. This resulted in a total of 63 pCT scans and 419 rCT scans. The rCT scans were taken on average 25 min before the treatment fraction.

DELINEATED VOLUMES

The average bladder volume on the pCT was about 300 cc and comparable between the different groups (Table 2). The bladder volumes in the rCT scans were significantly smaller compared to the pCT scan, except for the first week scans of the LCRT female patients (Figure 2). A significant negative time trend in rectal volume was present in the LCRT groups, more predominant in male than in female patients (Figure 2) with a rectal volume reduction of approximately 35% at the end of treatment. The average CTV volume on the pCT was 508 cc for female patients and 580 cc for male patients (Table 2).

SHAPE VARIATION

The local GM, ∑, and σ surface maps for each patient group were projected on the average CTV shape for visualization (Figure 3). The negative time trend in rectal volume resulted in a negative GM error at the upper-anterior border of the MesoRect for both LCRT groups. The GM error was significantly different from 0 for the male patients ($p < 0.01$) and borderline significant for the female patients ($p = 0.06$). Combining all LCRT patients resulted in a significant negative GM error of 0.5 cm ($p < 0.01$).

Table 1: Clinical and pathological characteristics

		5 x 5 Gy	25 x 2 Gy
Age (yrs)	Median (range)	65 (44-85)	64.5 (44-81)
Sex	Male	20	20
	Female	13	10
Distance from anus	< 5 cm	7	16
	5 – 10 cm	15	12
	> 10 cm	11	2
Resection type	LAR	26	17
	APR	7	13
cT-stage	T1	0	0
	T2	19	0
	T3	14	26
	T4	0	4
cN-stage	N0	22	3
	N1	9	17
	N2	2	10
cM-stage	M0	31	29
	M1	2	1

The ∑ was comparable between the groups. In general the maximum ∑, of approximately 1.0 cm SD, was found at the upper-anterior region of the MesoRect. Only for the male LCRT patients the maximum ∑ was somewhat smaller (0.8 cm SD). When comparing the male LCRT and SCRT ∑, differences

were only significant at the edges of the high variable upper-anterior CTV region of the LCRT group (Figure 4). Differences in ∑ between male and female LCRT were not significant. Random errors were comparable between the groups (no significant differences), similar in heterogeneity compared to the ∑, but slightly smaller (max 0.8 cm SD).

Table 2: Average volumes delineated/calculated on the planning CT (1SD)

	5x5 Gy		25x2 Gy	
	Female	Male	Female	Male
Bladder	322 cc (204)	301 cc (189)	298 cc (193)	243 cc (158)
Rectum	116 cc (49)	125 cc (56)	121 cc (28)	138 cc (52)
CTV	509 cc (154)	579 cc (101)	507 cc (110)	581 cc (93)
Current clinical PTV	1316 cc (290)		1484 cc (285)	
Proposed PTV (Table 3)	1107 cc (200)		1128 cc (127)	

MARGINS

To reach a D_{min} of 95% of the prescribed dose for 90% of the patients a factor α of 3.2 needed to be applied to the systematic errors (Figure 5). The rolling ball margins were calculated with factor α = 3.2 for SCRT and LCRT groups separately (Figure 6), because of the difference in GM error (Figure 3) and the significant difference in ∑ error between the male patients in both groups (Figure 4). The average PTV volumes were 997 cc (1SD = 184) and 944 cc (1SD = 127) for SCRT and LCRT ($p = 0.19$), respectively.

The CTV was divided into six sub-regions to define more practical orthogonal PTV margins (Table 3). The sub-regions were the earlier defined LN_L, LN_R, and presacral regions, and a division of the MesoRect in the sphincter region (caudal 4 cm) and an upper and lower half of the remainder of the MesoRect.

The proposed margins (Table 3) were also applied to the dataset to re-evaluate the accumulated D_{min} to the CTV, which resulted in a D_{min} of 95% of the prescribed dose to 94% of the patients. The average PTV volumes were 1233 cc (1SD = 198) and 1186 cc (1SD = 131) for SCRT and LCRT, respectively.

The actual clinical PTVs that were used during treatment had an average volume of 1316 cc (1SD = 290) and 1484 cc (1SD = 285) for SCRT and LCRT, respectively (Table 2). The proposed PTVs (Table 2), adapted to the same cranial and caudal border as the clinical PTVs, were significantly smaller with on average 1107 cc (1SD = 200) and 1128 cc (1SD = 127) ($p < 0.0001$) for SCRT and LCRT, respectively (Table 2).

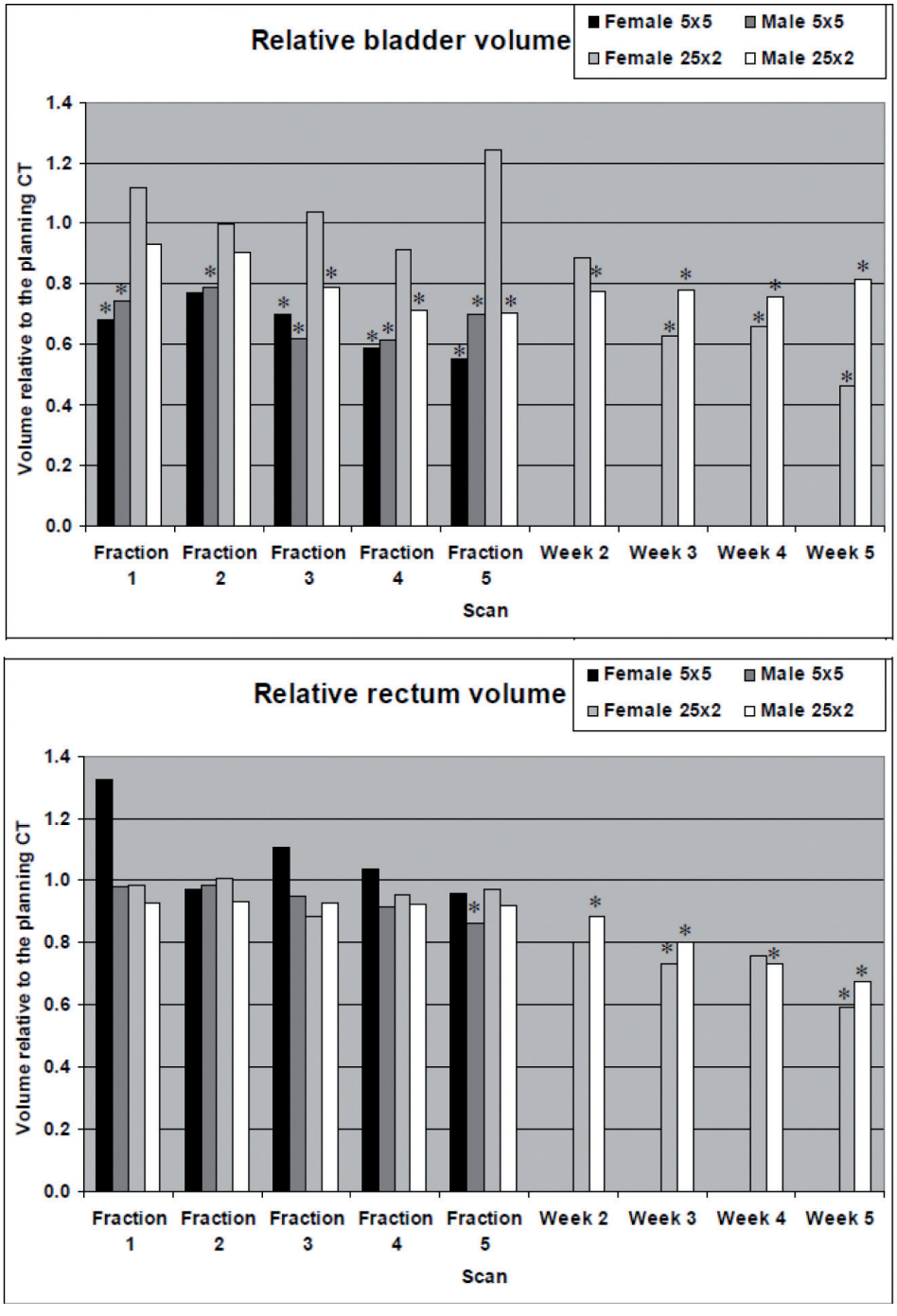

Figure 2: Relative bladder and rectum volume on the repeat CT scans with respect to the planning CT for the four groups. Bars indicated with a * were statistically significantly different from 1 ($p<0.05$ in a 2-sided z-test).

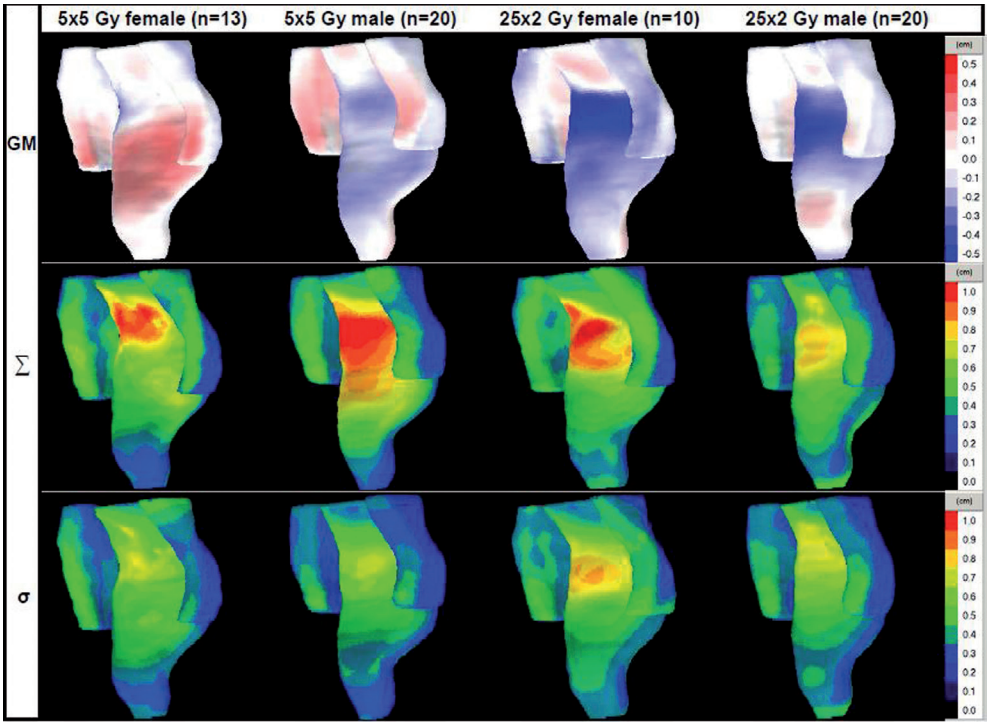

Figure 3: Left anterior view of the group mean (top), systematic (middle) and random (bottom) errors for the four groups of patients.

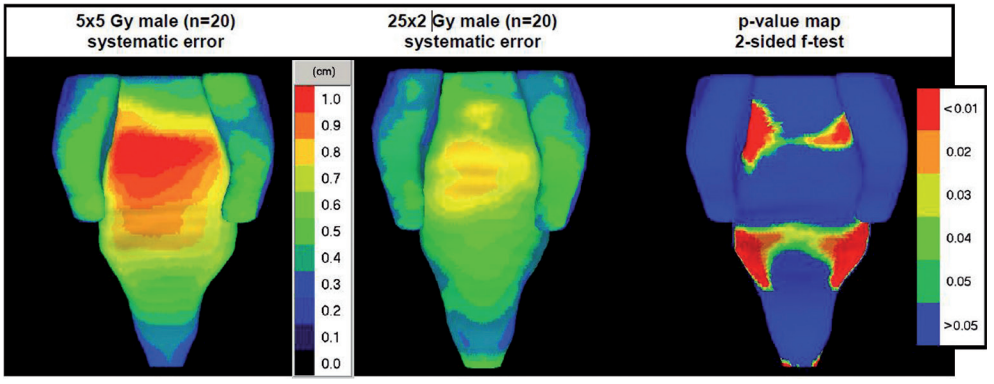

Figure 4: Anterior view of the systematic error for the 5x5 Gy male patients (left), 25x2 Gy male patients (middle) and the p-value results (right) of a locally calculated 2-sided f-test where only regions with systematic error differences of ≥ 0.2 cm were taken into account.

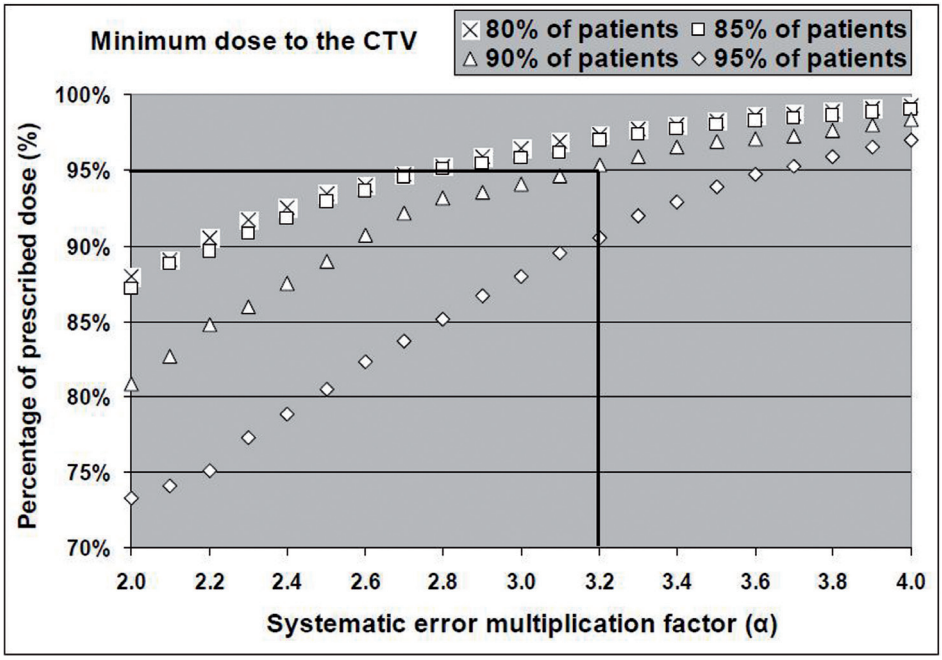

Figure 5: Minimum dose to the clinical target volume for the total dataset of 63 patients. This when applying $m_{PTV} = \alpha * \sum + 1.64 * \sqrt{(\sigma^2 + 0.32^2)} - 1.64 * 0.32 + GM$ when applying the ∑, σ and GM errors shown in Figure 1 for each group separately. With α=3.2, 90% of patients assured a minimum dose of 95% of the prescribed dose to the CTV.

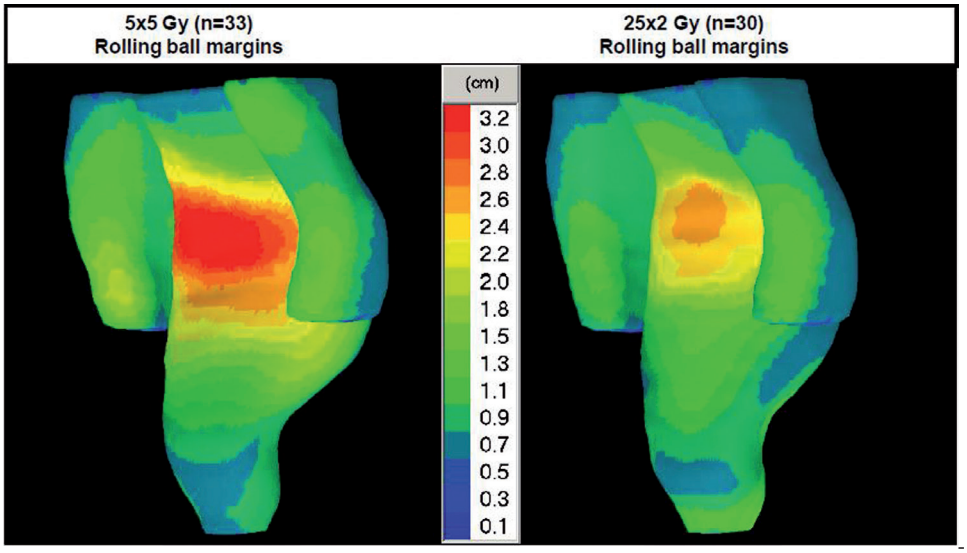

Figure 6: Locally defined rolling ball margins for the 5x5 Gy patients (left) and the 25x2 Gy patients (right).

Table 3: Required PTV margins for sub-regions of the CTV to assure a D_{min} of 95% of the prescribed dose to at least 90% of the patients.

25 x 2 Gy treatment schedule						
	Anterior	Posterior	Left	Right	Cranial	Caudal
LN_L	1.5 cm	0.7 cm	0.7 cm	1.0 cm	1.0 cm	1.0 cm
LN_R	1.5 cm	0.7 cm	1.0 cm	0.7 cm	1.0 cm	1.0 cm
Presacral	1.5 cm	0.7 cm	0.7 cm	0.7 cm	1.0 cm	1.0 cm
MesoRect upper half	**2.4 cm**	0.7 cm	0.7 cm	0.7 cm	1.0 cm	1.0 cm
MesoRect lower half	**1.5 cm**	0.7 cm	**0.7 cm**	**0.7 cm**	1.0 cm	1.0 cm
Sphincter	1.0 cm	**1.4 cm**	1.0 cm	1.0 cm	1.0 cm	1.0 cm
5 x 5 Gy treatment schedule						
LN_L	1.5 cm	0.7 cm	0.7 cm	1.0 cm	1.0 cm	1.0 cm
LN_R	1.5 cm	0.7 cm	1.0 cm	0.7 cm	1.0 cm	1.0 cm
Presacral	1.5 cm	0.7 cm	0.7 cm	0.7 cm	1.0 cm	1.0 cm
MesoRect upper half	**3.2 cm**	0.7 cm	0.7 cm	0.7 cm	1.0 cm	1.0 cm
MesoRect lower half	**1.8 cm**	0.7 cm	**1.0 cm**	**1.0 cm**	1.0 cm	1.0 cm
Sphincter	1.0 cm	**1.1 cm**	1.0 cm	1.0 cm	1.0 cm	1.0 cm

Bold numbers indicate the differences between both groups

DISCUSSION

The first aim of this study was to evaluate shape changes of the clinical target volume during pre-operative RT of early- and advanced-stage rectal cancer patients. With a dataset of 483 CT scans in a group of 63 patients we have shown that shape variation of the CTV is a substantial and heterogeneous geometric uncertainty. In long-course RT a volumetric negative time trend could be found for the CTV (Figure 2), as well as a significant difference in systematic error between the male patients in both groups (Figure 4).

The second aim was to establish PTV margins for CTV shape variation. With an adapted version of the van Herk margin recipe[64] it was shown that a multiplication factor of 3.2 for the systematic shape variation error could be used to reach a 95% D_{min} for 90% of the patients (Figure 5). The acquired locally defined PTV margins were pragmatically translated into clinically applicable margins for sub-regions of the CTV (Table 3) with sufficient CTV coverage and smaller PTV volumes compared to clinical PTVs.

CTV SHAPE VARIATION

In LCRT, Nuyttens *et al*[107] described the motion of the anterior border of the CTV, ranging from 0.4 cm SD at the anus, to 1.0 cm SD at 10 cm from the anus, which is similar to our results. Shape variation in LCRT was also described by Tournel *et al*[108] with a mean shift of 0.2 cm (1SD = 0.7 cm) and 0.04 cm

(1SD = 0.4 cm) in anterior and posterior directions, respectively. These results were averaged over all measurements on the cranio-caudal axis and over all patients, ignoring the heterogeneity of shape variation and the influence of inter-patient variation. The 0.7 and 0.4 cm SD in anterior and posterior directions do confirm that shape variation is substantial and heterogeneous.

In two previous studies we investigated the shape variation of the mesorectal part of the CTV during SCRT using CBCT scans[104;105]. We found heterogeneous shape variation with up to 0.8 cm ∑ and 0.7 cm σ at the anterior part of the mesorectum. In the current study repeat CT imaging was chosen instead of CBCT, because of better image quality and the ability to investigate the entire CTV. When comparing the systematic and random SD for the same regions in the current study, results are comparable in terms of heterogeneity and size. Where systematic errors in the CBCT studies were slightly larger for female patients[104;105], differences in the current study were not statistically significant.

One major significant difference comparing the four groups was the negative time trend in rectal volume for the LCRT (Figure 2). The negative time-trend in rectal volume was previously shown in repeat-CT studies on prostate cancer patients, indicating a RT dose-effect on rectal volume[112;113]. The LCRT patients in the current study also received chemotherapy, which might also have influenced the rectal volume.

In addition, we found a difference in systematic errors between both male groups (Figure 4), which might be explained by a difference in tumour location. In SCRT more upper rectal tumours were present, in LCRT more low seated. When evaluating the first week scans of all 63 patients divided into low-, mid-, and high seated tumours, high seated tumours showed statistically significant larger systematic errors at the anterior side of the CTV compared to mid- and low-seated tumours (data not shown). A more elaborated multi-variate analysis is needed, since tumour stages and treatment types were differently distributed in the three groups.

MARGINS

PTV margins to account for CTV shape variation in rectal cancer patients have been previously estimated by Tournel *et al*[108] and Brierly *et al*[102], for the mesorectal part of the CTV. In both papers the shape variation of the mesorectum was averaged over the cranio-caudal axis and over all patients. Doing so, the different effects of ∑ and σ on the D_{min} to the CTV were ignored, as well as the heterogeneity of systematic and random shape variation.

An important additional issue is that margins for shape variation should take the correlation of variation in different regions of the CTV into account[110;111]. Attempts have been made to estimate correlation by use of principal component analysis[114] and by a point distribution model based on corresponding points modelled using spherically parameterized and canonical aligned outlines[115]. Due to the complexity of these models and the lack of clinical implementation we have chosen for a more pragmatic approach calculating local ∑ and σ position variability and deriving a margin recipe by calculation of the CTV coverage.

The derived margin recipe included a ∑ multiplication factor α of 3.2 based on the total group of 63 patients. When estimating α for the 4 groups separately a range of 3.2, 2.8, 3.0, and 3.4 was found for LCRT male and female and SCRT male and female, respectively, with smaller statistical certainty. The small range of α with the extremes coming from the small female groups with only 10 and 13 patients suggests the applicability of the margin formula to other rectal cancer patients, but validation on a completely independent dataset is preferred. Note that applying a fixed multiplication factor to the heterogeneous systematic errors does not necessarily lead to the smallest possible PTV volumes. Increasing the multiplication factor in the least variable regions will substantially increase local coverage, while the PTV volume will only increase moderately. The gain in coverage could be used to decrease the multiplication factor in more variable regions, resulting in a larger reduction of the PTV volume.

In the current study ideal dose distributions were used to calculate CTV coverage. In clinical practice it is very hard to get the 95% isodose line on the edge of the PTV, especially in the anterior region where the horse-shoe shape results often in a somewhat broader dose distribution. The proposed clinical margins (Table 3) resulted in a 95% D_{min} to 94% of the patients, which was higher than the intended 90% of patients. These results do not include intra-fraction setup errors, intra-fraction shape variation, and delineation variation. We previously described intra-fraction setup errors in SCRT being 0.24, 0.10, and 0.06 cm ∑ and 0.22, 0.10 and 0.10 cm σ in LR, CC and AP directions, respectively[105]. We simulated the effect of intra-fraction setup errors on the proposed clinical margins (Table 3) using a Monte Carlo simulation. This resulted in a 95% D_{min} probability for 92% of simulated treatments, being closer to the intended 90%.

The difference in required margin between SCRT and LCRT patients was mainly due to the negative time trend in rectal and subsequent CTV volume in LCRT patients, for which the margin can simply be reduced.

Intra-fraction shape variation needs real-time imaging and is not easily performed. To our knowledge it has never been investigated and can therefore not be included in the analyses. However, we do assume that intra-fraction motion of the bladder and rectum is small compared to inter-fraction motion.

CTV delineation variation in rectal cancer is found to be comparable to shape variation errors when evaluating inter-observer variation[103;106]. In the current study observer variation was minimized by having one observer per patient, discussion of pCT delineations before delineation of the rCT scans, and availability of the pCT delineations during rCT delineation. Intra-observer variation using this approach was previously shown to be in the order of 0.2-0.3 cm SD for delineation of the Mesorectum on CBCT scans[104], for which the image quality is generally inferior to CT scans.

The proposed PTV margins (Table 3) are larger than current clinical margins of 1 cm. Despite the margin increase, PTV volumes were smaller compared to the clinical PTV volumes, with 16% and 24% volume reduction for SCRT and LCRT, respectively (Table 2). A strictly delineated CTV plus larger

margins therefore resulted in a smaller PTV, compared to observer based generous delineation of the CTV plus a 1 cm PTV margin. An advantage of using strict anatomical borders instead of observer dependent generous delineations for the CTV is the possible reduction in inter-observer variation[106].

It is important to realize that the derived results are mainly of advantage when using IMRT. With conventional 3- or 4-field conformal techniques dose outside the PTV will minimize the PTV volume reduction effect.

Another factor is that a large part of the CTV will contain only microscopic disease, at most. It is therefore questionable if the D_{min} of 95% of the prescribed dose is really needed for the entire CTV. Unfortunately, it is currently not possible to define the exact GTV within the CTV. Until further advances in GTV definition have been made it is unsafe to relax the constraints on the CTV coverage.

LIMITATIONS OF THE STUDY

The study is based on rCT data taken on average 25 minutes before the actual treatment fractions resulting in significantly smaller bladder volumes (Figure 2). In an earlier study we investigated the correlation between bladder and rectum volume changes and CTV shape variation[105], and demonstrated that shape variation is mainly driven by rectal filling, and not by bladder filling. Influence of the scan timing was therefore expected to be limited.

The number of female patients in the study was limited due to low accrual. Differences between male and female patients might therefore lack statistical power, as was already seen in the derivation of the α-factor. This is, however, the largest available study so far.

In order to combine data of different patients a corresponding point model was used based on fixed amount of slices and points per structure. Variation was measured perpendicular to the surface of the reference structures. This model is dependent on the definition of the different structures. Results are therefore only applicable to rectal cancer patients where the CTV is delineated according to the guidelines in the current study. All derived results are of course not applicable to patients meeting the exclusion criteria of previous surgery or RT in the pelvic area.

CONCLUSIONS

Clinical target volume shape variation is a major geometric uncertainty both in short- and long-course radiotherapy of rectal cancer patients. The shape variation was heterogeneous, with systematic shape variation ranging from 0.2 cm SD close to bony structures to 1.0 cm SD at the anterior-cranial end of the mesorectum. To assure 95% of the prescribed dose to the CTV for 90% of the patients $m_{PTV} = 3.2 * \sum + 1.64 * \sqrt{(\sigma^2 + 0.32^2)} - 1.64 * 0.32 + GM$ was established, where shape variation is determined perpendicular to the surface of planning CT CTV delineation. The derived margins were pragmatically translated to orthogonal margins for sub-regions of the CTV ranging from 0.7 cm margin in posterior direction up to 2.3 and 3.1 cm PTV margin at the upper anterior region of the mesorectum for long- and short-course RT, respectively. Anterior margins for long-course RT were smaller due to a significant

negative time trend in rectal volume. The proposed larger PTV margins in combination with a strict CTV delineation resulted in significant PTV reduction compared to the current clinical PTVs based on generous delineated CTVs and 1 cm PTV margin.

CHAPTER 4

Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer

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ABSTRACT

BACKGROUND

Capecitabine is an attractive radiosensitizer. In this study acute toxicity and surgical complications were evaluated in patients with locally advanced rectal cancer following total mesorectal excision (TME) after preoperative chemoradiotherapy (CRT) with capecitabine.

METHODS

Between 2004 and 2008, consecutive patients with clinical tumour category (cT) 3–4 (with a threatened circumferential resection margin or cT3 within 5 cm of the anal verge) or clinical node (cN) category 2 rectal cancer were treated with preoperative CRT (25 × 2 Gy, capecitabine 825 mg/m^2 twice daily, days 1–33). TME followed 6 weeks later. Toxicity was scored according to the Common Terminology Criteria (version 3.0) and Radiation Therapy Oncology Group scoring systems. Treatment-related surgical complications were evaluated up to 30 days after discharge from hospital using the modified Clavien–Dindo classification.

RESULTS

Some 147 patients were analysed. The mean cumulative dose of capecitabine was 95% and 98% of patients received at least 45 Gy. One patient died from sepsis following haematological toxicity. Grade 3–5 toxicity developed in 32 patients (21.8%), especially diarrhoea (10.2%) and radiation dermatitis (11.6%). There were no deaths within 30 days. Anastomotic leakage and perineal wound complications developed after 13 of 47 low anterior resections and 23 of 62 abdominoperineal resections. Surgical reintervention was required in 30 patients. Twenty-seven patients (20%) were readmitted within 30 days after initial hospital discharge.

CONCLUSION

Preoperative CRT with capecitabine is associated with acceptable acute toxicity, significant surgical morbidity but minimal postoperative mortality.

INTRODUCTION

Over the past two decades, local control of resectable rectal cancer has improved tremendously as a result of the introduction of total mesorectal excision (TME) and preoperative radiotherapy[26;116;117]. Where the circumferential resection margin (CRM) is threatened by tumour infiltration or extensive nodal involvement is present (N2), however, poor local control continues to pose a problem[21]. Randomized controlled trials[4;29;30;118] have shown that preoperative chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) leads to downstaging and downsizing, facilitating a higher probability of a tumour-free CRM[118] after resection in these patients. Possible drawbacks of this treatment regimen are surgical delay (especially in non-responders), overtreatment and toxicity due to the addition of chemotherapy.

Capecitabine, an oral prodrug of 5-FU, has been introduced over the past decade, and proven to be effective in the metastatic and adjuvant setting in colorectal cancer[119]. It mimics continuous 5-FU infusion. Advantages over continuous 5-FU include avoidance of complications associated with continuous intravenous administration and convenience to the patient. The question remains whether capecitabine is a worthy substitute as radiosensitizer in terms of toxicity, perioperative complications and efficacy. Phase II series[120-128] have shown that capecitabine is promising with respect to acute toxicity. However, in the literature little attention has been paid to the surgical complications following neoadjuvant CRT, especially when capecitabine is used as radiosensitizer. Anastomotic leakage following low anterior resection (LAR) remains an important and potentially fatal surgical complication. After neoadjuvant CRT, anastomotic leak rates of up to 27% have been reported[55], but this has not been reproduced in the randomized controlled trials[4;30;56]. Perineal wound complications after abdominoperineal resection (APR) represent a challenging management problem, with associated pain, unpleasant odour and unexpected drainage seriously affecting quality of life. Rates of 35% have been reported in patients receiving preoperative (chemo)radiotherapy[55;90] and historically in up to 57% of patients after APR in general[129].

These days, surgical complications are, among others, increasingly becoming healthcare quality outcome parameters[130]. To ensure uniform documentation and enable interinstitutional comparison, strict definition of complications is required. Surgical complications are mostly recorded as the 30-day complication rate, but sometimes manifest themselves more than 30 days after surgery[52], suggesting that the treatment-related complication rate is as important as the 30-day complication rate.

The aim of this study was to evaluate toxicity and surgical complications in patients with locally advanced rectal cancer following TME surgery after neoadjuvant CRT with capecitabine in a single institute. The results and use of definitions were compared with those reported by others.

METHODS

Between June 2004 and February 2008, consecutive patients with clinical tumour category (cT) 3–4 (T3 with a threatened circumferential resection margin or within 5 cm of the anal verge) or clinical node

category (cN) 2 primary rectal cancer were registered prospectively and treated with preoperative CRT in the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital. Magnetic resonance imaging (MRI) was used to evaluate tumour infiltration and the presence of lymph nodes larger than 1 cm or with clinical characteristics suspicious of metastases. Superficial tumours were excluded by endorectal ultrasonography (EUS). CT of the abdomen and X-ray or CT of the thorax were used to evaluate dissemination.

RADIOTHERAPY

Preoperative radiotherapy consisted of 50 Gy in 25 fractions on week days. The clinical target volume included the primary tumour and the mesentery with vascular supply, containing the perirectal, presacral and internal iliac nodes. The recommended upper border was at the level of the promontory. The perineum was included if an APR was planned, whereas the lower border was 3 cm above the anal verge if the planned operation was LAR. From April 2006 onwards, intensity-modulated radiotherapy (IMRT) substituted the three-field, three-dimensional conformal technique (90 versus 57 patients). Four patients received intraoperative brachytherapy with a 5-mm thick flexible intraoperative template. The radiation dose at 1 cm from the surface of the template was 7.5 or 10 Gy.

CAPECITABINE AS RADIOSENSITIZER

Capecitabine was administered orally and twice daily at a dose of 825 mg/m², on days of radiotherapy but also over weekends, adding up to 33 days of chemotherapy. From May 2007 onwards, patients were screened for a gene mutation (DPYD*2A mutation) which has been linked to a dihydropyrimidine dehydrogenase (DPD) enzyme deficiency and associated with severe 5-FU-related toxicity. One of the 48 patients evaluated showed this mutation and received a dose reduction.

SURGERY

All patients underwent surgery according to the TME technique, as advocated by Heald[131]. Surgery was performed in the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital or in one of ten regional hospitals (median 11 patients per hospital), approximately 6 weeks after neoadjuvant therapy had been completed. A diverting stoma was constructed at the discretion of the surgeon.

ACUTE TOXICITY AND POSTOPERATIVE COMPLICATIONS

During CRT, toxicity was evaluated once or twice weekly and subsequently discussed at a weekly multidisciplinary meeting. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC, version 3.0)[132]. Acute radiation-induced skin toxicity was scored according to the Radiation Therapy Oncology Group scoring system[133]. Postoperative surgical complications were scored using pre-specified definitions (Table 1). General complications were scored as cardiovascular, pulmonary, neurological or renal. The severity of surgical complications was scored using the validated modified Clavien–Dindo classification of surgical complications[134;135]. To

analyse treatment-related toxicity accurately, complications were not only evaluated during hospital admission but also during the first 30 days after discharge.

Table 1: Definition of treatment-related surgical complications (during admission and 30 days thereafter)

	Definition
Anastomotic leakage (LAR)	Any fluid collection around the anastomosis; clinical suspicion confirmed by surgery or diagnosed on CT or fluoroscopy.
Perineal wound complications (APR)	Wound dehiscence resulting from underlying infection, wound necrosis, prolonged admission after 3 weeks for wound care and professional wound care after discharge from hospital into the home environment.
Intra-abdominal abscess	Any fluid collection unrelated to the anastomosis or perineal wound.
Fistula	Enterocutaneous, enterovaginal, vesicovaginal, enterovesical connections.
Ileus	Need for (re)placement or delayed removal of nasogastric tube, absence of bowel sounds or defecation, all after 5 days following surgery.
Abdominal wound complications	Fascial dehiscence, superficial wound infection, open abdomen treatment, vacuum-assisted therapy.
Intestinal necrosis	Any bowel ischemia.
Urological	Ureter leakage, urinary incontinence, ureter stenosis, suprapubic or transurethral catheter-related complications, urosepsis.
Bleeding	Gastrointestinal haemorrhage, decrease in haemoglobin level directly after surgery treated conservatively with or without blood transfusion or by reintervention.

LAR, low anterior resection; CT, computed tomography; APR, abdominoperineal resection.

STATISTICAL ANALYSIS

The association between clinical variables and two key surgical complications (perineal wound complications and anastomotic leakage) was investigated using univariable analysis. The clinical variables included general patient and tumour characteristics, as well treatment-related variables such as any toxicity of grade 3 or more, at least grade 3 skin toxicity (only patients having APR), symptoms of obstruction requiring diversion before starting CRT, diverting stoma (only patients undergoing LAR), IMRT, duration of radiotherapy, interval between the beginning and end of radiotherapy, and resection and resection of a structure other than the mesorectum. Two-sided χ^2 or Fisher's exact test was used for categorical variables, and linear regression analysis for continuous variables. Because of the low number of events in each group, no multivariable analysis was performed. $P \leq 0.050$ was regarded statistically significant.

RESULTS

A total of 147 patients with locally advanced rectal cancer were analysed, 86 men and 61 women, with a median age of 64 (range 37–83) years. Patient and tumour characteristics are shown in Table 2. MRI-directed staging was implemented in 133 patients (90.5%); the remaining 14 were staged by EUS and/or CT of the abdomen.

Table 2: Patient and treatment demographics

		No. of patients (*n* = 147)*
Age (years)†		64 (37–83)
Sex ratio (M : F)		86 : 61
WHO performance status‡	0	86 (58.5)
	1	43 (29.3)
	2	10 (6.8)
	Unknown	8 (5.4)
Tumour distance from the anal verge (cm)	≤ 5	83 (56.5)
	6–10	46 (31.3)
	> 10	18 (12.2)
Clinical TNM classification§	cT2	2 (1.4)
	cT3	89 (60.5)
	cT4	56 (38.1)
	cN0	43 (29.3)
	cN1	63 (42.9)
	cN2	38 (25.9)
	cN unknown	3 (2.0)
	cM0	131 (89.1)
	cM1	16 (10.9)
Diverting stoma before CRT	Yes	54 (36.7)
	No	93 (63.3)
Surgery	Low anterior resection	47 (32.0)
	Hartmann procedure	22 (15.0)
	Abdominoperineal resection	62 (42.2)
	No resection	7 (4.8)
	No surgery	9 (6.1)
Diverting stoma after low anterior resection (*n* = 47)	Yes	35 (74)
	No	12 (26)
Pathological TNM classification (*n* = 131)‡	pT0	22 (16.8)
	pT1	6 (4.6)
	pT2	21 (16.0)
	pT3	75 (57.3)
	pT4	7 (5.3)
	pN0	83 (63.4)
	pN1	31 (23.7)
	pN2	15 (11.5)
	pN unknown	2 (1.5)

**With percentages in parentheses unless indicated otherwise; †values are median (range). ‡World Health Organization (WHO) classification[136]; International Union Against Cancer tumour node metastasis (TNM) classification, fifth edition[9]. CRT, chemoradiotherapy.*

CHEMORADIOTHERAPY AND ASSOCIATED ACUTE TOXICITY

The mean cumulative dose of capecitabine was 95% (range 32–100). Thirty-one patients (21.1%) requested or needed adjustments to the capecitabine intake; intake was stopped prematurely in 18 patients (12.2%) a median of 5 (range 1–23) days before the end of radiotherapy, interrupted in six (4.1%) for a median of 3 (range 1–12) days, and dose reduction was performed in seven patients (4.8%).

Some 98.0% of patients received at least 45 Gy radiotherapy. Six patients (4.1%) did not complete all radiotherapy fractions owing to gastric perforation after 44 Gy (1), parastomal abscess outside of the radiation portal after 48 Gy (1), (fatal) pancytopenia after 42 Gy (1) and patient's request (3, after 28 Gy in one patient and after 48 Gy in 2 patients).

Thirty-one patients (21%) experienced grade 3 toxicity; diarrhoea (10.2%) and radiation dermatitis (11.6%) were the most prominent (Table S1, supporting information). No grade 4 toxicity was documented, but one patient died (grade 5) in the last week of CRT from pancytopenia, mucositis and associated septic complications. The DPD enzyme activity was unknown in this patient. Patients receiving a diverting stoma because of obstructive symptoms (before CRT) experienced more toxicity of at least grade 3 than those with no stoma (18 of 54 versus 15 of 93; P = 0.016). No differences in grade 3–5 toxicity were observed between patients receiving IMRT versus three-dimensional conformal radiotherapy (P = 0.625).

SURGERY

After a median of 44 (range 22–87) days after the end of CRT, 138 of the 147 patients underwent a laparotomy. At laparotomy, resection was possible in 131 patients. Fig. 1 shows the types of surgery performed and reasons for exclusion.

HISTOPATHOLOGICAL EXAMINATION

Histopathological examination revealed microscopic tumour cells in the resection margin (R1) in seven (5.5%) of 127 patients for whom a report was available. The CRM was reported in 94 (71.8%) of 131 patients whose tumour was resected, and measured 1 mm or less in 16 (17%). In four of the 16 patients a tumour-positive lymph node determined the CRM (3 after sphincter-sparing surgery and 1 after APR). APR was associated with a higher overall rate of R1 resection (P = 0.050), whereas a trend was found for more CRM-positive resections (P = 0.082; including those with tumour-positive nodes determining the positive CRM). In an analysis of the subgroup in which the primary tumour extended to within 1 mm of the CRM, an abdominoperineal resection was also significantly associated with more CRM-positive resections (positive CRM in 10 patients after APR and 2 after sphincter-saving surgery; P = 0.011).

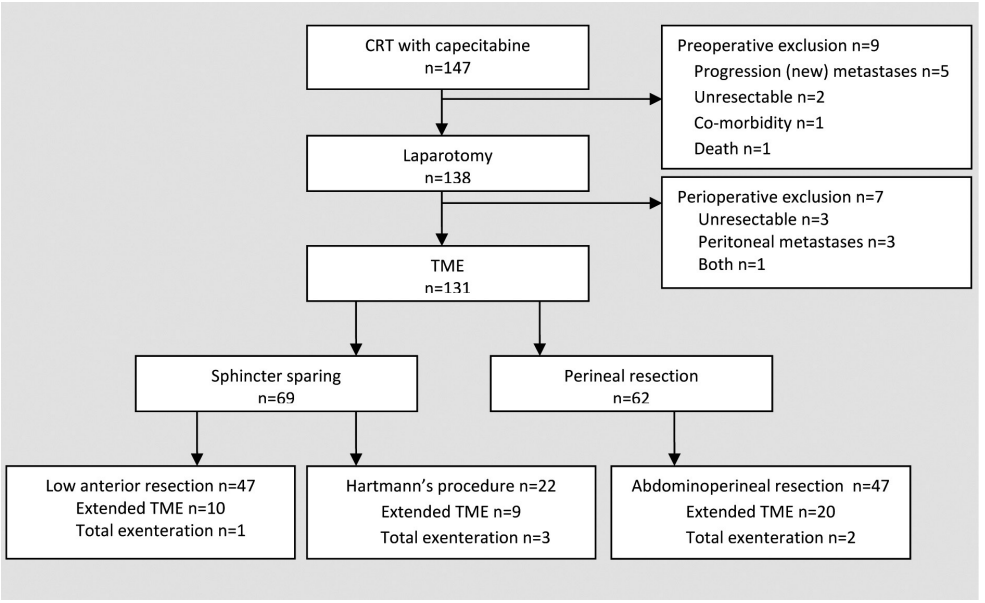

Figure 1: Flow diagram of treatment. Abbreviations: CRT: chemoradiotherapy, TME: Total mesorectal excision

TREATMENT-RELATED POSTOPERATIVE COMPLICATIONS

The median duration of the primary surgical admission for patients who underwent tumour resection was 14 (range 6–200) days, and 15 patients (11.5%) were admitted for more than 30 days. Twenty-seven (19.6%) of 138 patients who had a laparotomy were readmitted within 30 days after initial discharge from hospital. There were no deaths within 30 days after surgery. One patient died 3.5 months after an APR, as a result of enterocutaneous fistula following treatment for a large perineal defect. Surgical reintervention was required in 30 (21.7%) of 138 patients. Treatment-related complications are summarized in Table 3. Major general complications included myocardial infarction and a stroke in two patients with previous cardiovascular disease.

Anastomotic leakage developed in 13 (28%) of 47 patients following LAR, of whom 11 required surgical reintervention. In two of 13 patients, the anastomotic leakage manifested itself after discharge from hospital. Anastomotic leakage was distributed equally between men and women (7 of 26 and 6 of 21 respectively). Five of 12 patients without a diverting stoma developed anastomotic leakage versus eight of 35 with a diverting stoma (P = 0.269). Univariable analysis revealed that increasing age correlated with decreasing numbers of anastomotic leakages (P = 0.033).

A perineal wound complication developed in 23 (37%) of the 62 patients undergoing APR. In 11 of 23 patients, the perineal wound complication became evident after discharge from hospital. Eight of the 23 patients required surgical reintervention (including vacuum-assisted therapy). A poorer World

Health Organization (WHO) performance status[136] at diagnosis (2 versus 0–1) and extent of surgery (TME alone versus extended TME) were both associated with the development of perineal wound complications (P = 0.016 and P = 0.044 respectively). There were no differences in rates of perineal wound complications (P = 0.168), anastomotic leakage (P = 0.333) or other major postoperative complications (P = 0.850) between patients receiving IMRT versus three-dimensional conformal radiotherapy.

DISCUSSION

This study investigated the acute toxicity and postoperative complications of CRT with capecitabine followed by TME surgery in a relatively large series of patients with locally advanced rectal cancer. The preoperative CRT was tolerable, with a mean cumulative chemotherapy dose of 95% and 98% of patients receiving at least 45 Gy of the planned radiotherapy. The postoperative morbidity rate was significant, but this did not translate into postoperative mortality. Histopathological analysis showed a promising efficacy in this series characterized by 38.1% cT4 tumours, with an R1 resection rate of only 5.5%.

Nine phase II trials[120-128] were reviewed on toxicity and surgical complications (Table S2, supporting information). The trials described, incorporating capecitabine as radiosensitizer in more than 50 patients, generally included all cT3–4 N0–2 disease, whereas in the present series the treatment was limited to those with a CRM at risk of incomplete resection and those with extensive nodal disease (cN2). Capecitabine was generally taken continuously and 59–99% received the dose as planned, as in the present series (78.9%). With grade 3–4 toxicity developing in 21.1% of patients during CRT, the results are comparable with those of other phase II studies incorporating capecitabine (range 11–23%). With the intention of using capecitabine to optimize radiosensitivity, prescribing capecitabine on days of radiotherapy only could be considered an option in the future, to further optimize tolerability.

Anastomotic leakage is a potentially fatal surgical complication after LAR. In the present series, no patient died as a result of an anastomotic leak, but it was diagnosed in 28% of patients undergoing LAR. This seems much higher than reported rates of about 10% in the randomized controlled trials[4;26;29;30;52;56;60;90;96;117;118;137;138] evaluating radiotherapy or CRT with 5-FU (Table S3, supporting information). A plausible reason for this difference could be the more advanced nature of the tumours in this series. Kerr and colleagues[55] have recently described a retrospective series of 189 patients, with similar disease characteristics (50% cT4) and definitions, and reported anastomotic leakage in 27% of patients after LAR. Interestingly, they found a relationship between decreasing rates of anastomotic leakage and increasing interval between CRT and surgery, and suggested delaying surgery beyond 8 weeks. As only five patients in the present series had a delay beyond 8 weeks, this finding could not be confirmed. Of the nine phase II trials[120-128] reviewed (Table S2, supporting information), only four reported anastomotic leakage rates[120;121;124;127]. Rates ranged between 0 and 3%, suggesting a different way of scoring, especially as none of the studies defined anastomotic leakage. Another possible

Table 3: Treatment-related complications (events during admission and 30 days thereafter)

	No. of patients analysed	Complications							
		Total	Grade 1	Grade 2	Grade 3a	Grade 3b	Grade 4a	Grade 4b	Grade 5
Surgical complications									
Anastomotic leakage	47	13 (28)		1 (2)	1 (2)	11 (23)			
Perineal wound complications	62	23 (37)	1 (2)	14 (23)		8 (13)			
Intra-abdominal abscess	138	7 (5.1)	1 (0.7)		5 (3.6)	1 (0.7)			
Fistula	138	10 (7.2)	1 (0.7)			8 (5.8)			1 (0.7)
Ileus	138	28 (20.3)	24 (17.4)		2 (1.4)	2 (1.4)			
Abdominal wound complications	138	15 (10.9)	9 (6.5)			6 (4.3)			
Intestinal necrosis	138	5 (3.6)				5 (3.6)			
Urological	138	15 (10.9)	7 (5.1)	2 (1.4)	2 (1.4)	4 (2.9)			
Bleeding	138	6 (4.3)		5 (3.6)	1 (0.7)				
Other									
Intravenous line infection	138	3 (2.2)		3 (2.2)					
Gastrointestinal perforation	138	2 (1.4)				2 (1.4)			
Stoma complications	123	2 (1.6)				2 (1.6)			
Total events		129	43	25	11	49			1
Patients with ≥ 1 surgical complication	138	69 (50.0)	34 (24.6)*				35 (25.4)†		
General complications									
Cardiovascular	138	9 (6.5)		8 (5.8)			1 (0.7)		
Pulmonary	138	9 (6.5)		9 (6.5)					
Neurological	138	4 (2.9)	2 (1.4)	1 (0.7)			1 (0.7)		
Total events		22	2	18			2		
Patients with ≥ 1 general complication	138	19 (13.8)	17 (12.3)*				2 (1.4)†		
Patients with ≥ 1 complication	138	75 (54.3)	39 (28.3)*				36 (26.1)†		

*Postoperative complications were scored according to the modified Clavien–Dindo severity classification[134;135]. *Grades 1 and 2; †grades 3–5.*

explanation involves the (discretional) use of a diverting stoma to protect the anastomosis. Recently, a randomized controlled trial[52] with clinical anastomotic leakage as primary endpoint randomized patients after uncomplicated rectal cancer surgery to a diverting stoma or not. A significant reduction in clinical anastomotic leakage rate from 28 to 10% was demonstrated with the use of a diverting stoma. Furthermore, two recently published meta-analyses[139;140] and a pooled analysis[51] have combined published data from randomized controlled trials and showed a reduced rate of anastomotic leakage with a diverting stoma. In the present study, the anastomotic leak rate was reduced from five of 12 to eight of 35 with the use of a diverting stoma, although the difference was not significant, possibly owing to the small numbers.

Impaired postoperative wound healing is a well-recognized risk following radiotherapy[141]. In the present series, 37% of patients developed perineal wound complications, which is in line with rates of up to 35% in the preoperative radiotherapy arms in randomized controlled rectal cancer trials (Table S3, supporting information). However, in these studies, as well as in the phase II studies reviewed incorporating capecitabine as radiosensitizer (Table S2, supporting information), the reported perineal wound complication rates vary enormously. In the present study, both poor performance status (WHO performance status 2) at diagnosis and extent of surgery were associated with perineal wound complications, suggesting a role of both patient reserves and size of the surgical wound in wound healing. Another important issue is the fact that a perineal wound may seem to heal normally initially, but subsequently manifest itself as a complication after discharge from hospital. Almost half of the 23 perineal wound complications were diagnosed or became evident at readmission within 30 days after discharge. This underlies the importance of thorough follow-up in this patient group and may warrant adaptation of currently used definitions in clinical trials.

Regarding the definition of anastomotic leakage and perineal wound complications, it is remarkable how the reported definitions vary in the reviewed phase II studies[123;125;126] and European randomized trials in rectal cancer (Tables S2 and S3, supporting information)[4;24;30;52;56;60;90;96;117;137;138]. The scope of a definition and the way it is implemented largely determine the reported complication rate. It is comprehensible that surgical complications are underreported when they are not well defined or do not form the primary endpoint of a (large) multicentre study. Over the years, the instigators of the modified Clavien–Dindo classification have validated a severity classification of complications in a cohort of 6336 patients and confirmed its value in an international survey among 144 surgeons. This classification was used in the present study and showed that almost 40% of the 129 surgical events experienced required surgical, radiological or endoscopic (re)intervention under general anaesthesia (grade 3b). Of these, only 39% were due to anastomotic leakage or perineal wound complications.

Of equal importance in allowing interinstitution comparison is the definition per complication. For example, anastomotic leakage may be reported incorrectly as a percentage of all laparotomies instead of those with an anastomosis, as was the case in two phase II studies[125;126]. Only recently, the International Study Group of Rectal Cancer[142] published an extensive review on all reported definitions of anastomotic leakage, proposing a definition similar to that used in the present series with a grading

system consisting of three grades (grade C requiring a laparotomy). However, no period in which the complications were to be scored was mentioned. In general, the high readmission rate within 30 days after discharge suggests that treatment-related complications (up to 30 days after discharge) could be a more realistic representation of morbidity after CRT and surgery than in-hospital or 30-day morbidity.

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Table S1: Chemoradiotherapy-related toxicity in 147 patients

	Grade 3	Grade 4	Grade 5	Total events
Haematological				3
Anaemia	2 (1)			
Pancytopenia			1 (1)	
Non-haematological				35
Diarrhoea	15 (10)			
Pain	6 (4)			
Mucositis	3 (2)			
Dehydration	3 (2)			
Anorexia	2 (1)			
Gastric perforation	1 (1)			
Obstruction	1 (1)			
Nausea	1 (1)			
Vomiting	1 (1)			
Hand and foot syndrome	1 (1)			
Rash	1 (1)			
Radiotherapy related				17
Skin dermatitis (RTOG)	17 (12)			
Other toxicity				3
Ileus	1 (1)			
Transient ischaemic attack	1 (1)			
Stoma revision	1 (1)			
Total events	57	0	1	58
No. of patients with grade 3 or more toxicity				32 (22)

Values in parentheses are percentages. RTOG, radiation Therapy Oncology Group[133].

Table S2: Phase II studies (with more than 50 patients) evaluating toxicity after capecitabine-based chemoradiotherapy and surgery

Reference	Design	*n*	Definition of locally advanced rectal cancer	RT (Gy)	Capecitabine (mg/m²)	Patient group characteristics	Grade 3–4 toxicity (% of patients)	Radiation dermatitis grade ≥ 3 (%)	Diarrhoea grade ≥ 3 (%)	Myelotoxicity grade ≥ 3 (%)	Received full dose of CT (%)	Received full dose of RT (%)	Postop. complications (%)	Anastomotic leak (%)	Perineal wound complications (%)
Craven *et al*[120]	II	70	CRM at risk or T3–4 < 5cm from AV	45 (25 × 1.8)	900 b.i.d.*	T4: 16% < 5 cm: 46%	11	NR	NR	NR	89	96	NR	NR	NR
Rodica-Maricela *et al*[127]	II	98	Stage 2–3	50 (25 × 2)	500 b.i.d.	> 65 years	NR	NR	20	19	NR	88	NR	NR	NR
Krishnan *et al*[126]†	II	54	T3–4 or N+	45 (25 × 1.8) + B 5 × 1.5	825 b.i.d.	T4: 4%	23	9	2	74	59	98	6	3	4
Kim *et al*[124]	II	133	T3–4, < 8 cm from AV	45 (25 × 1.8) + B 3 × 1.8	825 b.i.d.	T4: 2%	10	NR	2	7	99	100	4	NR	NR
Velenik *et al*[128]‡	II	57	Stage 2–3	45 (25 × 1.8)	825 b.i.d.	< 5cm: 49%	NR	35	4	2	NR	98	44	2	21
de Paoli *et al*[121]	II	53	T3–4, N0–2	45 (25 × 1.8) + B 3 × 1.8	825 b.i.d.	T4: 13%	11	4	2	10	72	96	NR	NR	NR
Kim *et al*[125]§	II	95	T3–4 or N+, < 10 cm from AV	46 (23 × 2) + B 1 × 4	825 b.i.d.	T4: 27%	NR	0	3	2	98	97	9	3	6
Dupuis *et al*[123]¶	II	51	T3–4 or N+, < 13cm from AV	45 (25 × 1.8)	825 b.i.d.	T4: 2%	NR	4	6	NR	90	96	12	0	6
Dunst *et al*[122]	II	96	T3–4 or N+	45 (25 × 1.8) + B 3 × 1.8	825 b.i.d.	T4: 40% N2: 18%	NR	1	7	18	NR	97	NR	NR	NR
Present series	R	147	T4, T3 with CRM at risk or < 5 cm from AV or cN2	50 (25 × 2)	825 b.i.d.	T4: 38%	22	12	10	2	79	96	54	28	37

**On week days only. On week days and weekends in all other studies. †Grade 3–4 haematological toxicity rate includes grade 3 lymphopenia of unknown significance (70 per cent). Wound complications (2 of 51) were reported for all laparotomies: wound dehiscence, infection and abscess. ‡Delayed wound healing reported for all laparotomies. §Anastomotic leakage within 60 days after surgery. Wound complications (6 of 94) were reported for all laparotomies: delayed healing, wound dehiscence, infection and abscess within 60 days. ¶ Wound complications (3 of 50) were reported for all laparotomies: delayed wound healing, perineal abscess. RT, radiotherapy; CT, chemotherapy; phase II study; CRM, circumferential resection margin; T, tumour category; AV, anal verge; b.i.d., twice daily; NR, not reported; (c)N, (clinical) node category; B, boost; R, retrospective.*

Table S3: European (randomized controlled) trials in rectal cancer

RCT name/origin	Design	cT4 tumours (%)	No. of patients	Anastomotic leakage (%)	Definition	Perineal wound complications (%)	Definition	Mortality (%)
Polish trial[56;118]	CRT *versus* 5 × 5 Gy	NR	305	9 *versus* 11	30-day anastomotic leakage requiring reoperation	21 *versus* 29	30-day perineal wound healing delay and/or peritoneal wound infection not requiring surgery	1
EORTC[29;137]	CRT *versus* 45 Gy RT only	12 *versus* 11	1012	NR	NR	NR	NR	2 *versus* 1
FFCD trial[4]	CRT *versus* 45 Gy RT only	10 *versus* 11	762	7 *versus* 8	Fistula after LAR	NR	NR	2
Scandinavian LARCS[96]	CRT *versus* 50 Gy RT only, in locally non-resectable T4	74 *versus* 83	207	NR	NR	3 *versus* 0	Delayed perineal wound healing	0
German trial[30]	Preop. *versus* postop. CRT	6 *versus* 3	799	11 *versus* 12	30-day anastomotic leakage rate	10 *versus* 8	30-day sacral wound healing	1
Dutch TME trial[26;60]	5 × 5 Gy + TME *versus* TME only	NR	1530	11 *versus* 12	Clinical anastomotic leak, suspicion after contrast enema, abscess around anastomosis during first admission	29 *versus* 18	Perineal wound dehiscence and infection during first admission	4 *versus* 3
Swedish Rectal Cancer Trial[24]	5 × 5 Gy surgery *versus* surgery only	NR	1168	NR	NR	NR	NR	4 *versus* 3
MRC-CR07[90]	5 × 5 Gy *versus* surgery only (+ adjuvant CRT on indication)	NR	1350	9 *versus* 7	Clinical anastomotic leak at 1 month	35 *versus* 22	Non-healing perineum not otherwise specified	2 *versus* 2
Uppsala trial[117]	5 × 5 Gy *versus* 60 Gy RT adjuvant for subset of patients	NR	471	17 *versus* 17	Anastomotic dehiscence	33 *versus* 18	Perineal wound sepsis	3 *versus* 4
Lyon R90-01[138]	Short *versus* long interval after 13 × 3 Gy	2 *versus* 0	201	18 *versus* 17	Anastomotic complication: fistula, intra-abdominal abscess, general peritonitis	NR	NR	3 *versus* 4
Swedish trial[52]	Diverting stoma *versus* no stoma after uncomplicated distal or mid-rectal cancer surgery	NR	234	10 *versus* 28	Symptomatic leakage only. Peritonitis caused by leakage from any staple line, rectovaginal fistula, and pelvic abscess without radiologically proven leakage mechanism included	NA	NA	NR

RCT, randomized controlled trial; (c)T, (clinical) tumour category; CRT, chemoradiotherapy; NR, not reported; EORTC, European Organization for Research and Treatment of Cancer; RT, radiotherapy; FFCD, Fédération Francophone de la Cancérologie Digestive; LAR, low anterior resection; LARCS, locally advanced rectal cancer study; TME, total mesorectal excision; MRC, Medical Research Council; NA, not applicable.

CHAPTER 5

Tumour regression grading after CRT for locally advanced rectal cancer: a near pathologic complete response is a poor prognostic factor

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ABSTRACT

BACKGROUND

After preoperative chemoradiotherapy (CRT) for rectal cancer, some rectal tumours undergo complete tumour regression (pCR). Clinically undetectable residual tumour deposits or pathologic lymph nodes may remain in the mesorectum. The consequences thereof are still unknown. The aim of this study was to report histopathological effects of CRT and factors affecting outcome in a uniformly treated series of strictly defined locally advanced rectal cancer (LARC) patients.

METHODS

Between 2004-2008, 107 consecutive patients with cT3 (threatening the mesorectal fascia or <5 cm from the anal verge), cT4 or cN2 rectal cancer were treated with preoperative CRT (25x2 Gy with capecitabine) and TME 6-8 weeks later. Central revision of histopathology followed and tumour regression grade (TRG) was scored with 4-tiers (pCR, near-pCR, response, no response). Uni- and multi-variable Cox regression were performed to identify prognosticators.

RESULTS

With a median follow-up of 44 months, the 3-year distant metastasis-free interval (DMFI), DFS rate and OS rate were 82%, 73% and 87%, respectively. TRG consisted of 20% pCR, 11% near-pCR, 55% response and 14% no response. 6/21 patients with a pCR harboured nodal metastases. 5/12 patients with a near-pCR had ypT3 disease, while 6 harboured node metastases. Near-pCR was associated with a relatively poor outcome: 5/12 patients developed distant metastases. ypN and TRG were powerful discriminators of DMFI, DFS and OS.

CONCLUSION

pCR is associated with excellent outcome, while patients with a near-pCR fare poorly. The high number of near-pCR with ypT3 or ypN1/2 disease demonstrates that "wait and see" in LARC patients should be applied with extreme care.

INTRODUCTION

The treatment of rectal cancer has evolved immensely over the last 2 decades, resulting in improved local control and overall survival. The importance of tumour cells observed close to the inked circumferential resection margin[68] (CRM ≤ 1 mm) in predicting local control and overall survival has led to refinement of the surgical technique and a neo-adjuvant approach. In the treatment of locally advanced tumours, where the risk of a positive CRM is high, short-course radiotherapy (SCRT) followed directly by total mesorectal excision (TME) will not suffice[27;90;143]. These patients require preoperative downsizing of the tumour with fluoropyrimidine-based chemoradiotherapy (CRT) and delayed TME for adequate local control[4;29;30]. Downsizing after SCRT followed by delayed TME surgery has also been observed[144] and is currently being evaluated in the Stockholm III trial. Following improvements in local control, patient outcome in rectal cancer is nowadays determined by distant metastases, which are diagnosed in 30% of patients[75]. Adjuvant systemic chemotherapy seems to be the obvious means of attacking micro-metastases, but evidence for its use in rectal cancer is sparse and inconsistent[29;38;75;79-81].

The increasing use of neoadjuvant therapy in rectal cancer provides new challenges for pathologists. Tumours appear to respond heterogeneously to neoadjuvant therapy; mechanisms governing response or resistance remain unclear. For instance, certain tumours react with the formation of fibrosis completely replacing the tumour cells, while in others scattered tumour deposits are left behind. Other tumours are replaced by acellular mucin lakes. Unfortunately, some tumours are non-responsive. The histopathological regression of tumour to the CRT is assessed by a semi-quantitative scoring of the relative proportion of residual tumour to stromal fibrosis, the tumour regression grade (TRG)[74]. It is conceivable that after CRT a highly responsive tumour is associated with superior treatment outcome. Published series[38] demonstrate excellent outcome in those 8-24% of the cases in which no viable primary tumour cells are found in the resection specimen after CRT (pathologic complete response or pCR). The results after more intensive combination-regimens, however, have been disappointing, with more adverse effects[33;145]. Therefore, radiotherapy to a dose of 45-50 Gy with concurrent daily capecitabine, an oral prodrug of 5-FU, seems to have become the standard of care.

The concept of a pCR after CRT questions the need for additional resection. The group of Habr- Gama *et al*[39] have published multiple series on a non-operative "wait and see" policy in those patients in whom no residual tumour is detected at clinical assessment after CRT. Meticulous clinical, endoscopic and radiological follow up was implemented to guarantee a sustained clinical complete response (cCR). Using this policy, a locoregional failure rate of only 3% was reported in a series[39] of distal rectal cancer patients (20% cT2, 70% cT3, 11% cT4 and 23% cN+), which is comparable to those with a pCR after resection. These excellent results have been confirmed in another series[40]. However, data are scarce regarding those in which the cCR is not sustained, and in which salvage resection is required due to locoregional failure. The risks of a non-operative (or local) treatment include under-treatment or treatment delay in those with residual lymph node metastases and those with undetectable tumour deposits in the mesorectum.

Differences in patient selection, indications for the treatment, definition of locally advanced rectal cancer (LARC), preoperative regimens, but also lack of standardized TME and pathology make comparisons between different series difficult. The aim of this study was to report histopathological effects of CRT and factors affecting outcome in a uniformly treated series of strictly defined LARC patients.

PATIENTS AND METHODS

PATIENTS

In the period between June 2004 to February 2008 a total of 147 consecutive patients with LARC, defined as a cT4 tumour, a cT3 tumour <5 cm from the anal verge or threatening the mesorectal fascia (MRF) on magnetic resonance imaging (MRI) or cN2 disease, underwent preoperative CRT in the Netherlands Cancer Institute. MRI was used to evaluate tumour infiltration and the presence of lymph nodes larger than 1 cm or with clinical characteristics suspicious of metastases. A CT-scan of the abdomen and X-ray or CT-scan of the thorax were used to evaluate dissemination.

PREOPERATIVE CHEMORADIOTHERAPY

Preoperative radiotherapy consisted of 50 Gy in 25 fractions on week days. The clinical target volume included the primary tumour and the mesentery with vascular supply, containing the perirectal, presacral and internal iliac nodes. The recommended upper field border was at the level of the promontory. The perineum was included if an abdominoperineal resection (APR) was planned, whereas the lower border was 3 cm above the anal verge if the planned operation was low anterior resection (LAR). From April 2006 onwards, intensity-modulated radiotherapy (IMRT) substituted the three-field, three-dimensional conformal technique. Four patients received intra-operative brachytherapy using a 5-mm thick flexible intra-operative template. The radiation dose at 1 cm from the surface of the template was 7·5 or 10Gy. Capecitabine was administered orally and twice daily at a dose of 825 mg/m^2, starting on the first day and ending on the last day of radiotherapy, including weekends. The mean cumulative dose of capecitabine was 95% (range 32–100) of the prescribed dose, while 98% of patients received at least 45 Gy.

SURGERY

Surgical resection followed 6-8 weeks later in the Netherlands Cancer Institute or in one of ten regional hospitals. Resection was performed according to the principles of TME and adapted upon indication: an APR or Hartmann procedure for distal tumours, LAR for mid or proximal tumours and exenterative surgery for infiltration into surrounding organs or structures. Preoperative clinical assessment of response with endoscopy or imaging was not standard treatment. Of 147 patients receiving neo-adjuvant CRT, 138 were considered fit for surgery and underwent laparotomy after completion of neo-adjuvant therapy. Of these, 131 were considered resectable intra-operatively. A further 19 patients were excluded because of synchronous distant metastases while in 5 patients pathology slides were

not available prohibiting pathological review. Thus, 107 patients were included for the analysis. Adjuvant chemotherapy is not standard of care in the Netherlands; four patients received adjuvant chemotherapy as part of a prospective trial.

HISTOPATHOLOGICAL ANALYSIS

Routine macroscopic and microscopic examination of the resection specimens was performed in the pathology laboratories of the participating hospitals according to the principles proposed by Quirke[68]. All H&E-stained slides of the resection specimens together with the original pathology reports were reviewed. Overall, a median of 14 blocks per patient were examined, while for pCR patients the median was 16 blocks. In 13 patients deeper levels were evaluated to facilitate accurate scoring. By reaching consensus two investigators (SB and MS), blinded to patient outcome, revised the histopathological diagnosis and scored additional tumour characteristics. In 37 (34%) cases uncertainties or discrepancies were resolved by consulting an independent colorectal pathologist (IN). The specimen was staged according to the 5th TNM staging system[146], as is common practice in the Netherlands. Tumour characteristics included histological type and grade of differentiation, invasion depth (ypT), lymph node status (ypN), (circumferential) resection margin status, presence of acellular mucin lakes, presence and size of tumour deposits, intra- and extramural venous invasion, lymphangio-invasion and perineural growth. Tumour deposits (TD) were defined as tumour nests demonstrating discontinuous growth from the primary tumour, with mesorectal fat or fibrosis separating the TD from the growth front of primary tumour. Furthermore, tumour nests sectioned as possible lymph nodes but with no signs of a lymph node or with a recognizable capsule but without a bordering layer of lymphocytes were considered a tumour deposit.

A tumour was considered mucinous when the mucinous proportion was ≥ 50%, and was not graded to further extent. Due to limited numbers venous invasion, lymphangio-invasion and perineural growth were grouped together into one factor, “neuro-vascular invasion”. Since no photos were available for revision/scoring of the completeness of the specimen, this information was not explored.

Tumour regression was scored using a simple and practical 4 tier system as illustrated in Figure 1: 1) pCR, pathological complete response without residual primary tumour; 2) near pCR, only isolated residual tumour cells or small groups of residual tumour cells; 3) response: stromal fibrosis outgrowing tumour and 4) no response: no regression or those with stromal fibrosis outgrown by tumour.

LOCAL RECURRENCE, DISTANT METASTASES AND OVERALL SURVIVAL

Distant metastases were defined as systemic metastases of rectal cancer to another organ, to distant lymph nodes stations or by dissemination to the peritoneal surface. Local recurrence was defined as a radiological or histopathological determination of rectal cancer recurrence in the pelvis. Follow-up information for local recurrence or distant metastasis and overall and disease-free survival was gathered by a comprehensive review of all patients files and contacting the patient’s general practitioner. Distant metastasis-free interval (DMFI) was defined as the time between surgery and

distant metastasis or last assessment. Disease-free survival (DFS) was defined as the time between surgery and the first event (local recurrence, distant metastasis, second primary or death) or last assessment. OS was defined as time between surgery and death or last assessment.

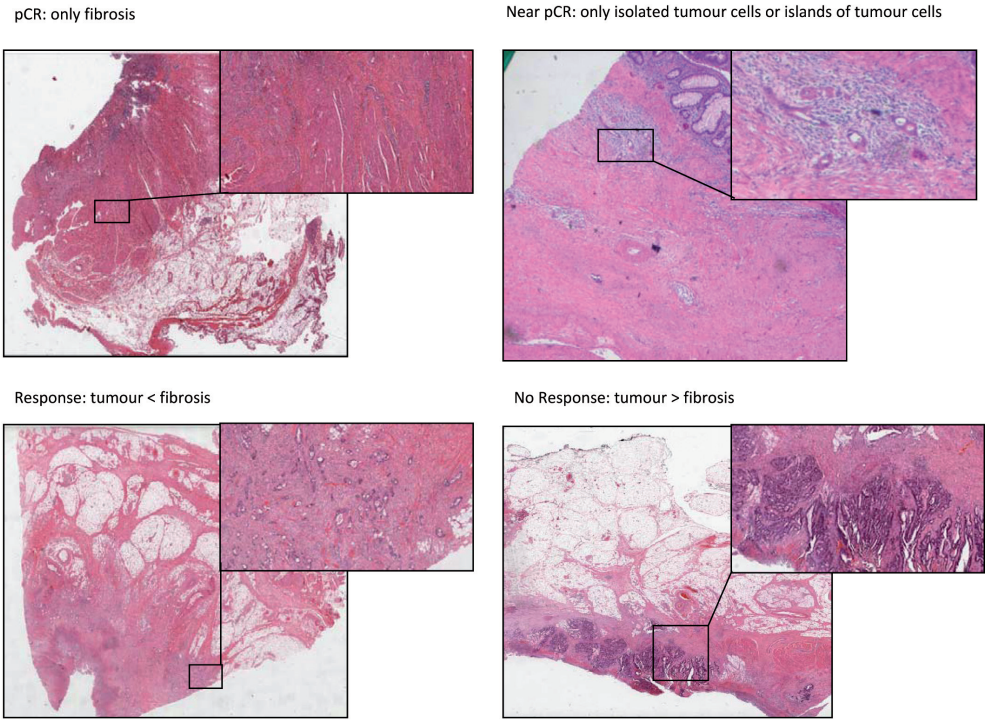

Figure 1: Microscopic illustration of different grades of tumour regression.

STATISTICAL ANALYSIS

Associations between pre- or post-treatment factors and tumour regression was assessed using linear by linear or Fisher exact tests, as appropriate. The associations between these factors and DMFI, DFS and OS was performed using Cox proportional hazard regression. The proportional hazards assumption was tested using partial Schoenfeld residuals. Survival curves were constructed using the Kaplan-Meier technique. In the multivariable regressions, missing data on pre- or post-treatment factors were imputed using the largest subgroup. The level of significance was set at 0.05 in all analyses.

RESULTS

PATIENT DEMOGRAPHICS

The study involved 107 patients, 64 male and 43 female with a median age of 64 years (range 38-82). Baseline characteristics are listed in Table 1. On MRI, in 62 patients the tumour (58%) was located in

the distal rectum, 42 (39%) patients were staged as cT4 and in 29 (27%) patients extensive lymph node involvement was suspected (cN2). Forty (37%) patients underwent a LAR, 15 (14%) patients underwent a Hartmann procedure, while in 52 (49%) patients an APR was required due to close relation to the sphincter complex. Total exenteration was required in 6 patients, while partial exenterative surgery was performed in 25 patients.

RESPONSE TO CHEMORADIOTHERAPY

Table 2 presents associations between tumour regression and other histopathological factors. Downstaging to ypT0-2 occurred in 43 (40%) patients. After CRT, lymph node metastases were still present in 40 (37%) patients. Tumour deposits were identified in 28 (26%) patients, the majority of whom had a single deposit (median = 1, range = 1-12). The median size of the deposits was 7 mm (range 0.5-30 mm). Resection resulted in a CRM + rate (defined as primary tumour or lymph node metastases ≤ 1 mm from the CRM) of 15%. In 11 patients the primary tumour defined the positive CRM, while in 5 patients a positive node defined the positive CRM. In 8 of the 16 patients the inked margin was infiltrated (CRM = 0 mm) by the primary tumour while in 2 patients a positive lymph node infiltrated the CRM.

Twenty-one (20%) patients achieved a pathologic complete response (pCR) of the primary tumour and in 12 (11%) patients a near pCR was observed. Seven of the pCR patients and 6 of the near pCR patients initially had a cT4 tumour. Response was seen in an additional 59 (55%) patients, while in 15 (14%) patients the tumour showed no response to CRT. Of note, 6 of 21 (29%) pCR patients had mesorectal lymph nodes metastases.

In the univariate analysis no pre-treatment factors (age, cT, cN, and distance from the anal verge) were significantly associated with tumour regression. Regression grade was associated with decreasing invasion depth (ypT, $p<0.001$) and the absence of neurovascular invasion ($p=0.03$). A positive CRM occurred more frequently in those showing no regression ($p=0.01$). Neither TRG nor ypT were associated with pathological node status ($p=0.47$ and $p=0.24$, respectively).

ASSOCIATION BETWEEN RESPONSE AND OUTCOME

After a median follow-up period of 3.7 years (95%CI 3.3-4.2), 87 (81%) patients were alive, of whom 75 (70%) were free of cancer, 5 (5%) developed a local recurrence only, 19 (18%) developed a distant metastasis only and 4 developed both (2 synchronously, 1 local recurrence first and 1 distant metastasis first). Four patients died due to other causes. The overall 3-year distant metastasis-free interval (DMFI) was 82%, the disease free survival (DFS) rate was 73% and overall survival (OS) rate was 87%. Neither preoperative tumour nor nodal stage influenced outcome (DMFI, DFS or OS). Table 3 displays the associations between histopathological features and outcomes. Due to small numbers (n=9) of local recurrence, no further analysis regarding prognosticators was performed.

Table 1: Baseline patient demographics

Demographics (n=107)		n	%
Age	Median	64	(38 - 82)
Sex	Male	64	60
	Female	43	40
WHO performance status*	0	69	64
	1	24	22
	2	8	7
	Missing	6	6
Distance from anal verge	0-5 cm	62	58
	5-10 cm	30	28
	>10 cm	15	14
Clinical tumour stage (cT)	0	-	-
	1	-	-
	2	1	1
	3	64	60
	4	42	39
Clinical node stage (cN)	0	31	29
	1	46	43
	2	29	27
	Missing	1	1
Interval CRT and TME	3-5 weeks	16	15
	5-7 weeks	65	61
	>7 weeks	26	24

**WHO Performance status: 0 – Asymptomatic, 1 – Symptomatic but completely ambulatory 2 – Symptomatic, <50% in bed during the day.*

Table 2: Uni-variable associations between histopathological factors and the 4 tier tumour regression grade (TRG).

		Total n=107		pCR n=21		Near pCR n=12		Response n=59		No Response n=15		p-value
		n	%	N	%	n	%	n	%	n	%	
ypT												<0.001
	T0	21	20	21	100	-	-	-	-	-	-	
	T1	3	3	-	-	2	17	1	2	-	-	
	T2	19	18	-	-	5	42	13	22	1	7	
	T3	59	55	-	-	5	42	42	71	12	80	
	T4	5	5	-	-	-	-	3	5	2	13	
ypN												0.47
	N0	67	63	15	71	6	50	37	63	9	60	0.26*
	N1	28	26	5	24	4	33	15	25	4	27	
	N2	12	11	1	5	2	17	7	12	2	13	
Tumour Deposits												0.15
	No	79	74	17	81	10	83	43	73	9	60	
	Yes	28	26	4	19	2	17	16	27	6	40	
Circumferential resection margin												0.19
	> 1mm	90	85	21	100	10	83	50	85	9	64	
	≤ 1mm	16	15	-	-	2	17	9	15	5	36	
	Missing	1	-	-	-	-	-	-	-	1	-	
Histological type												0.42
	Adenocarcinoma	76	88	-	-	9	75	54	92	13	87	
	Mucinous	10	12	-	-	3	25	5	8	2	13	
	Not applicable	21	-	21	-	-	-	-	-	-	-	
Grade of Differentiation												0.11
	Well/moderate	59	78	-	-	8	89	43	80	8	62	
	Poor/undiff	17	22	-	-	1	11	11	20	5	39	
	Not applicable**	31	-	21	-	3	-	5	-	2	-	
Neuro-vascular invasion***												0.03
	No	69	80	-	-	11	92	49	83	9	60	
	Yes	17	20	-	-	1	8	10	17	6	40	
	Not applicable	21	-	21	-	-	-	-	-	-	-	
Acellular Mucin Lakes												0.38
	No	71	66	15	71	8	67	40	68	8	53	
	Yes	36	34	6	29	4	33	19	32	7	47	

** p value for pCR versus "the rest" **all mucinous tumours and pCR. *** lymphangio-invasion, perineural growth, intra- and extramural venous invasion.*

The tumour regression grade (TRG) was a significant prognosticator of the DMFI (p=0.002). In addition, ypN (p<0.0001), presence of tumour deposits (p<0.001), ypT (p=0.002), acellular mucin lakes (p=0.007), histological type (p=0.01) and grade of differentiation (p=0.02) were all significantly associated with DMFI. TRG (p=0.02) and ypT (p=0.004) both retained their prognostic value for DMFI after adjusting for ypN. Due to the limited number of patients with distant metastases (n=23), no further multivariable analysis towards independent prognostic factors for DMFI could be performed.

The TRG was a significant prognosticator of the DFS (p=0.001). Post-treatment pT (p=0.02) and ypN (p<0.001), presence of tumour deposits (p=0.004), histological type (p=0.03), grade of differentiation (p=0.03), acellular mucin lakes (p=0.03), and CRM (p=0.02) were also significantly associated with DFS. After adjusting for ypN, TRG (p=0.02) and ypT (p=0.04) retained prognostic value.

Regarding overall survival, TRG was a powerful prognosticator (p<0.001). Histopathological factors predicting OS included ypN (p=0.004), CRM (p=0.04), TD (p=0.01) and histological type (p=0.03), but only TRG retained significance after adjusting for ypN.

EXCELLENT OUTCOME IN THE PCR GROUP

In Figure 2, time to recurrence, second primary or death has been displayed for the separate TRG groups, illustrating that, with a median follow-up of 3.7 years (95% CI: 2.8 - 4.7), the 21 patients with a pCR have an excellent outcome, with no local recurrences and only one (5%) patient developing a distant metastasis. This patient was one of the 6 patients with a pCR still harbouring lymph node metastases.

POOR PROGNOSIS IN THE NEAR PCR GROUP

A summary of all near pCR patients is presented in Table 4. Three-year DMFI, DFS and OS rates for near pCR patients were 65%, 50% and 67% respectively, which are comparable to those with no response (64%, 60%, 79%). Of the 12 patients with a near pCR, 7 died (4 within two years), of whom 6 with disease progression. Five near pCR patients developed distant metastases. After 3 years, one near pCR patient developed a local recurrence on the anastomosis. In 6 (50%) of the 12 near pCR patients, nodal metastases were still present (of which 2 ypN2). In 5 patients isolated tumour cells were found invading the fat (ypT3), while in 2 patients the CRM was positive.

Table 3 Uni-variable associations between time-to-event outcomes and histopathological factors. The second p-value denotes tests adjusting for ypN.

			3-year DMFI			3-year DFS			3-year OS		
		n	%	95% CI	p-value	%	95% CI	p-value	%	95% CI	p-value
TRG					0.002			0.001			<0.001
	pCR	21	95	87-100	0.02	84	69-100	0.02	95	86-100	0.002
	Near pCR	12	65	42-100		50	28-88		67	45-99	
	Response	59	86	77-95		76	65-89		91	83-99	
	No response	15	64	44-95		60	40-91		79	61-100	
ypT					0.002			0.02			0.16
	0-2	43	93	85-100	0.004	80	68-93	0.04	90	82-100	0.23
	3-4	64	75	65-87		68	57-81		85	77-95	
ypN					<0.001			<0.001			0.004
	N0	67	91	84-98		83	73-93		95	90-100	
	N1	28	73	58-92		60	44-82		75	60-93	
	N2	12	58	36-94		44	21-92		75	54-100	
Tumour deposits					<0.001			0.004			0.01
	No	79	90	84-97	0.17	80	71-90	0.47	92	86-98	0.57
	Yes	28	61	45-82		53	37-75		75	61-93	
CRM					0.11			0.02			0.04
	> 1mm	90	84	76-92	0.85	76	67-86	0.35	89	83-96	0.54
	≤ 1mm	16	73	54-100		51	30-87		75	57-100	
Histological type					0.01			0.03			0.03
	Adenoca	76	83	75-92	0.26	74	64-85	0.29	87	80-96	0.24
	Mucinous	10	50	27-93		38	16-87		70	47-100	

			3-year DMFI			3-year DFS			3-year OS		
		n	%	95% CI	p-value	%	95% CI	p-value	%	95% CI	p-value
Grade of differentiation					0.02			0.03			0.11
	Well/moderate	59	88	80-97	0.33	79	69-91	0.33	91	83-99	0.46
	Poor/undiffer	17	64	43-96		57	37-88		76	58-100	
Neuro-vascular invasion					0.54			0.81			0.54
	No	69	80	71-90	1	71	60-83	0.76	87	79-95	0.84
	Yes	17	76	59-100		66	44-98		78	59-100	
Acellular Mucin lakes					0.007			0.02			0.67
	No	71	88	80-96	0.1	78	68-89	0.16	89	82-97	0.91
	Yes	36	72	59-88		62	48-81		83	72-96	

Table 4: Patients with a pathologic near Complete Response

Pt	cTNM	Distance from anal verge	Type of resection	ypTNM	CRM status	TD present	Neuro-vascular invasion	Type	Diff	Acellular mucin lakes	Progression	Location distant metastasis or 2nd primary	Status
1	cT4N0	<5 cm	LAR	ypT3N0	> 1 mm	-	No	Adenoca	Well	No	LR anastomosis	2nd primary: non-small cell lung carcinoma	Dead
2	cT4N2	<5 cm	APR	ypT3N2	0 mm (node)	1	No	Mucinous		Yes	M+, LR-	Inguinal, iliac, retroperitoneal nodes	Dead
3	cT4N0	<5 cm	APR total exent.	ypT3N0	> 1 mm	-	No	Adenoca	Well	No	M+ ,LR-	Glandula parotis with mandibular destruction	Dead
4	cT4N1	<5 cm	APR	ypT2N1	> 1 mm	-	No	Adenoca	Well	No	No progression		Alive
5	cT3N2	6-10 cm	LAR	ypT3N1	> 1 mm	1	No	Mucinous		Yes	M+, LR-	Peritoneal and lung	Dead
6	cT3N0	<5 cm	APR	ypT2N0	> 1 mm	-	No	Adenoca	Well	Yes	No progression		Alive
7	cT4N2	<5 cm	APR post exent.	ypT3N0	> 1 mm	-	No	Mucinous		Yes	M+, LR-	Bone and Inguinal nodes. 2nd prim: facial melanoma	Dead
8	cT3N1	6-10 cm	Hartmann	ypT2N2	0.5 mm (node)	-	No	Adenoca	Well	No	No progression	2nd primary: colon transversum pT3N1	Alive
9	cT4N1	<5 cm	APR post exent.	ypT2N0	> 1 mm	-	No	Adenoca	Well	No	No progression		Alive
10	cT3N2	<5 cm	APR	ypT1N1	> 1 mm	-	No	Undiffer	-	No	No progression		Dead
11	cT3N1	<5 cm	APR	ypT1N0	> 1 mm	-	No	Adenoca	Well	No	No progression		Alive
12	cT3N2	>10 cm	LAR	ypT2N1	> 1 mm	-	Yes	Adenoca	Well	No	M+, LR-	Liver and lung	Dead

Pt: patient number, cTNM/pTNM: clinical/pathological Tumour Node Metastases stage according to TNM 5th edition. LAR: Low anterior resection. APR: abdominoperineal resection. CRM: Circumferential resection margin. TD: tumour deposit. Diff: differentiation of tumour (well versus poorly). M+: distant metastasis. LR: local recurrence. – : absent. + : present.

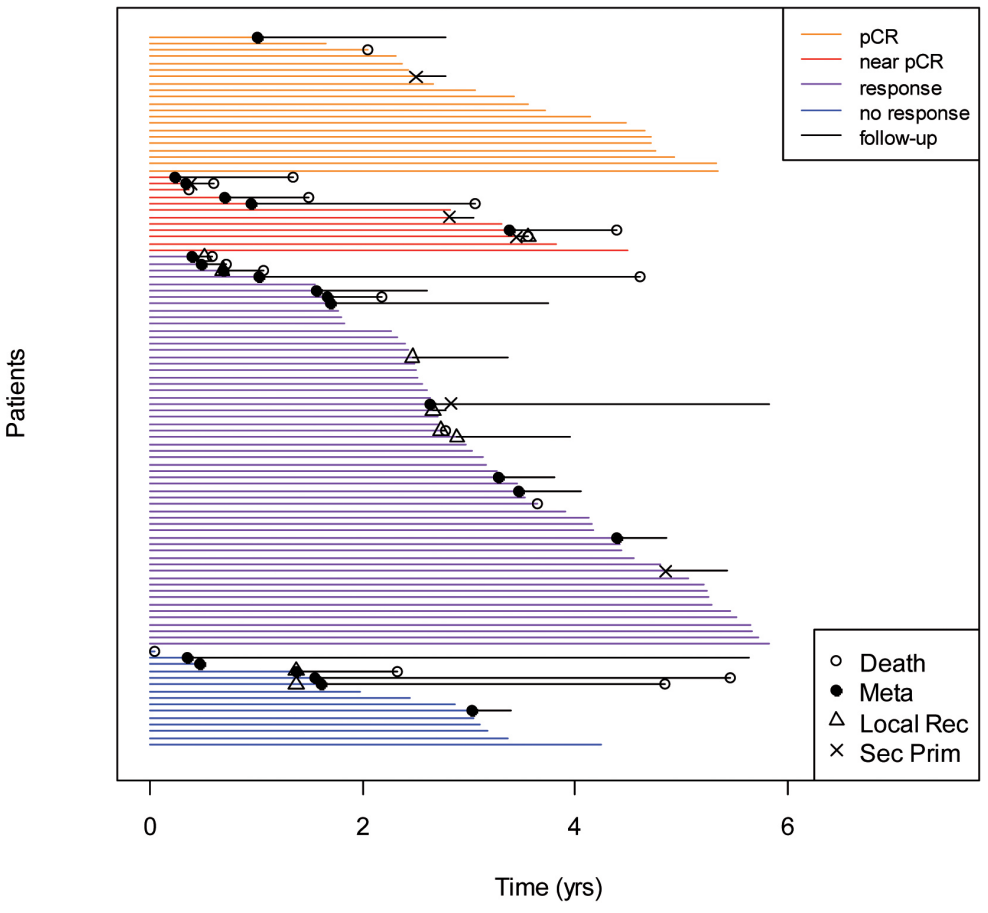

Figure 2: Survival durations and event types for the four different TRG groups.

DISCUSSION

In this series of 107 patients with LARC, defined as cT4, cT3 threatening the MRF or <5 cm from the anal verge or cN2 on MRI, we confirm the excellent outcome in those with a pathological complete response after CRT and curative resection. However, the subgroup with a near complete response seems to fare poorly. Furthermore, we identified prognosticators for the development of distant metastases.

Mechanisms governing the heterogeneous response to neoadjuvant CRT and their effects on patient outcome remain unclear. In our series, 20% of patients achieved a pCR after CRT. One third of these were clinical T4 tumours. Patients with a pCR have an excellent outcome with no local recurrence while one patient developed a distant metastasis. This is in line with the literature[38;147] and raises the question whether more aggressive neoadjuvant strategies should be implemented to increase

the pCR rate and improve prognosis. Some studies have shown an increase in pCR rate with a longer interval between radiotherapy and surgery. So far, however, it remains unclear whether this translates into an outcome similar to patients with pCR after shorter intervals. Other options include increasing the radiotherapy dose or adding radiosensitizing drugs[33] or biologicals[148]. Neo-adjuvant chemotherapy prior to CRT might be an attractive option to simultaneously decrease distant metastases[149].

Provided that clinical assessment after CRT is accurate and robust the concept of a pCR has introduced opportunities for less radical surgery, such as local excision of the tumour and even for omission of surgery all together (the "wait and see" policy). Avoiding surgical morbidity and subsequent decrease in quality of life as a result of organ resection are obvious advantages of this approach. However, the "wait and see" policy has only been analysed in a few single centre series[39;40], is questioned by others[41;150;151] and therefore requires further validation. Since the clinical imaging modalities at hand still lack diagnostic accuracy, omitting surgery in patients with undetected (nodal) disease may worsen prognosis. This study confirms these concerns and demonstrates potential risks involved in LARC patients treated with CRT in particular. In line with Gosens *et al*[71] studying a similar population of LARC patients, but in contrast to others[152;153] nodal response after CRT was not related to primary tumour regression in our series, suggesting independent modes of response to CRT. Even in patients with a ypT0, nodal metastases were still present in 6/21 (29%) patients in our series of strictly defined locally advanced cases and in 5-19% of patients in the literature[8;38;71;150;151;154]. In a recently published series of ypT0-2 patients after CRT, Park *et al*[151] demonstrated that 17% of ypT1 and 21% of ypT2 patients still harboured nodal disease after TME. The impact on prognosis of not removing these lymph nodes, as is the case with both the "wait and see" policy and local excision procedures, is as yet unknown.

Another major concern is the effect of microscopic tumour deposits in the mesorectal fat, since those cannot be assessed by re-staging endoscopy and are difficult to discriminate from fibrosis on MRI. A recent publication by Duldulao *et al* demonstrated that 17 of 53 ypT3-4 patients after CRT revealed tumour cells in deeper layers but not in the mucosa or submucosa[150]. In a review[41], of 208 patients with a cCR approximately 30% were actually confirmed to be a pCR after resection, indicating the need of more accurate re-staging. Of note, the prognostic importance of these tumour deposits after neoadjuvant therapy is unclear[155;156] and a topic of on-going discussion. Tumour deposits form part of the pathological T or N stage in the TNM 5th edition, depending on their size, and have been correlated with poor outcome[155]. Their presence showed to be a firm predictor of distant metastases in our series, possibly indicative of more aggressive tumour biology.

The relatively poor outcome of the near pCR cases in our study is not a universal finding. Others have reported excellent outcomes in near pCR patients[152;157] or in those with >95% regression[158] and even reported outcome comparable to those with a pCR. In our series, 12 patients exhibited a near complete response of the primary tumour with only isolated tumour cells or islands of cells spread throughout the bowel wall and mesorectal fat (Table 4). In contrast to others, these near pCR patients were associated with an unexpectedly poor outcome (DMFI, DFS and OS), which was comparable to those not responding to CRT at all. No single prognosticator could be identified, but half of the near

pCR patients harboured nodal metastases while in 5 patients isolated tumour cells were found in the mesorectal fat (ypT3). In recent series poor outcome is also reported in near pCR: Gosens *et al*[71] reported an overall survival of 66% after a near complete response which was comparable to the poor responders, while Rödel[153] described a similar trend of decreased disease- and distant metastasis-free survival for their group of good responders (73%) as compared to their moderate responders (83%). The prognosis of those with a near pCR is probably multi-factorial and this, once again, underlines the potential risk involved using a "wait and see" policy.

In the last decade, local control in LARC patients has improved immensely with an intensified neoadjuvant approach[4;29;30] and further refinement of surgical technique[159-162]. However, few studies focus on distant metastases after CRT, which develop in up to 39%[163] of LARC patients and have become the event governing outcome. In our series, distant metastases developed in 21% of patients indicating the need of a more thorough understanding of factors predicting DMFI. Two studies have reported a correlation between TRG and distant metastases. Rödel *et al*[153] reported a univariate association between TRG, using a 3-tiered regression grading system, and distant metastases. Vecchio *et al*[152] reported a series of 144 patients with mainly cT3 tumours receiving neoadjuvant therapy (84% CRT) and observed that the four TRG groups, as used in the present series, significantly predict those at risk for distant metastases. TRG, together with ypT and ypN stage, retained prognostic power in their multivariable analysis. This is in line with our observations: when adjusting for ypN, we observed that both ypT and TRG were still significantly associated with a decreased DMFI, suggesting independent prognostic value of TRG next to nodal status.

To our knowledge this is the largest cohort of well-defined LARC patients selected using state of the art staging, consistently receiving 25x2 Gy RT and capecitabine followed by TME 6-8 weeks later. Central revision of the resection specimens assured quality of histopathology thereby minimizing inter-observer variability. Apart from shortcomings inherent to retrospective analyses, other shortcomings include the absence of a full model multivariable analysis due to low number of events and that no correction for multiple-testing was performed, thereby categorizing our data as hypothesis generating and in need of further validation.

In conclusion, CRT followed by TME for LARC patients is effective and leads to an acceptable outcome. Histopathological assessment of tumour regression after CRT can, amongst other factors, be used to predict the risk for distant metastases. Near complete responders have a significantly worse outcome compared to complete responders. We demonstrate the relevance of tumour deposits and residual lymph node metastases in near pCR patients in particular and stress that a "wait and see" policy should be applied with extreme care. A significant subgroup of patients with LARC develop distant metastases after CRT and TME, demonstrating room for improvement, for instance with the implementation of neoadjuvant chemotherapy during the delay to surgery as is currently being investigated in the RAPIDO trial (ClinicalTrials.gov: NCT01558921).

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CHAPTER 6

Evaluating long-term attachment of two different endoclips in the human gastrointestinal tract

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ABSTRACT

BACKGROUND

The spectrum of clinical indications for the use of endoscopic clips (endoclips) is rapidly expanding. As retention rates of endoclips have only been reported in animal models, we evaluated the long-term attachment of two types of endoclips in the human gastrointestinal tract.

METHODS

In this prospective observational study, endoclips were placed and followed-up during endoscopies or using fluoroscopic images as part of a prospective feasibility study evaluating external beam radiotherapy (EBRT, wk 1-3) followed by high dose rate brachytherapy (HDRBT with an endoluminal applicator once a week for three weeks, wk 9-11) in medically inoperable rectal cancer patients. Initially, type and number of endoclips were chosen randomly and later refined to 1 Resolution® clip (Microvasive) proximal and 2 Quickclips® (Olympus) distal to the tumour. Nine consecutive patients, included between September 2007 and August 2008, were analysed. Retention rates were evaluated over three different observational periods (period 1: pre-HDRBT (wk -2 - 8), period 2: during HDRBT (wk 9-11) and period 3: post-HDRBT (wk 12-16).

RESULTS

In this study a total of 44 clips were placed during endoscopy, either at the beginning or at the end of period 1. The Resolution clip had a higher overall retention rate than the Quickclip ($P = 0.01$). After a median period of 81 days after placement (in period 1), long-term retention rates for the Resolution clip and Quickclip clip were 67% and 35%, respectively.

CONCLUSION

The Resolution clip has a high retention rate and is useful in situations where long-term attachment to the human gastrointestinal mucosa is warranted.

INTRODUCTION

In 1975, Hayashi *et al* were the first to describe the metallic endoscopic clip as an alternative means to control bleeding by mechanical pressure[164]. Since then, design and clinical indications have been refined. Nowadays, endoscopic clips are frequently used for haemostasis of arterial non-variceal bleeding of the upper gastrointestinal tract[165;166]. Other reported indications for endoscopic clip placement include the fixation of enteral feeding tubes[167], stent anchorage[168;169] and the management of small fistulas, perforations and anastomotic leaks[170]. Utilizing their radiopaque characteristics, endoclips have recently been used to mark tumours or anatomical structures to facilitate intervention radiology[47], to locate the tumour peroperatively[50] and to delineate tumour volume for radiotherapy[48;49].

Several types of endoscopic clips are commercially available. Most studies involve those from Olympus (Olympus Ltd., Tokyo, Japan), available in preloaded (Quickclip) and reloadable devices (HX-5L). Once the clip has been opened, re-positioning is not possible as the jaws cannot be closed and reopened. The Resolution clip (Microvasive, Boston Scientific Corp, Massachusetts, US) has the ability to reopen its jaws for repositioning, which may result in superior positioning and tissue grasping.

The ability of an endoclip to remain attached for a longer period could facilitate procedures in which a tumour needs to be located routinely during the treatment period or when the clip anchors feeding tubes or stents. Retention rates have, however, only been evaluated in canines and pigs and have not yet been reported in the human gastrointestinal tract. The aim of this study was to evaluate the long-term attachment of two endoclips, the Quickclip and the Resolution clip, to human rectal mucosa.

MATERIAL AND METHODS

STUDY POPULATION

The 9 consecutive patients analysed in this study were patients with medically inoperable rectal cancer who participated in a prospective feasibility study in the Netherlands Cancer Institute. The primary objective of this on-going study is to evaluate the feasibility of external beam radiation therapy (EBRT) followed by high-dose rate endorectal brachytherapy (HDRBT) as definitive treatment in patients not suitable for surgery due to co-morbidity, old age or for those refusing surgery. The study gained ethical approval from the Medical Ethics Committee of the Netherlands Cancer Institute. Written informed consent was obtained from all patients. Patient accrual commenced in September 2007.

TREATMENT PROTOCOL

The treatment regimen (Figure 1) consists of 39 Gy administered in 13 fractions of 3 Gy over 3½ weeks. After a further six weeks, HDRBT is applied once every week for three weeks. HDRBT dose level will be elevated (starting at 5 Gy/fraction) after every 6 patients depending on experienced toxicity. HDRBT is applied using an endorectal applicator (Oncosmart®, Nucletron, Veenendaal, the Netherlands)

consisting of a flexible tube with 8 channels (Figure 2). The applicator is 2 cm in diameter and is inserted via the anus prior to each brachytherapy treatment.

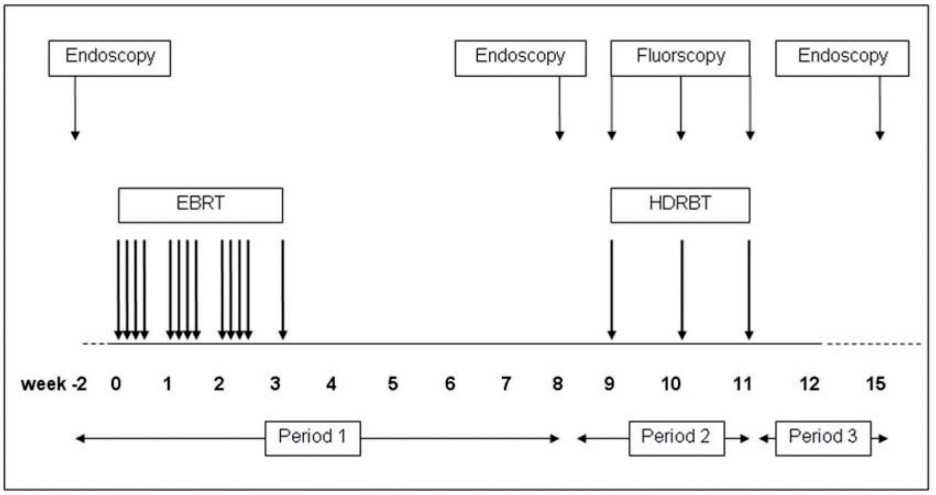


Figure 1 Treatment plan: Patients first receive external beam radiotherapy followed by high dose rate brachytherapy. Abbreviations: EBRT: external beam radiotherapy. HDRBT: high dose rate brachytherapy. wk: week

6

ENDOCLIPS

The rectal tumour was marked (Figure 3a) with Quickclips (Olympus Ltd., Tokyo, Japan) and/or Resolution (Microvasive, Boston Scientific Corp, Massachusetts, US) endoclips to facilitate tumour localization during the HDRBT procedure. Endoscopy was performed before EBRT (baseline), before HDRBT (week 8-9) and after HDRBT (week 16-17). The tumour was marked before EBRT and, if necessary, additionally (when clips had been dislodged) before HDRBT. Initially, type and number of endoclips were chosen randomly. Later on, this was refined to one Resolution endoclip at the proximal and two Quickclips at the distal border of the tumour.

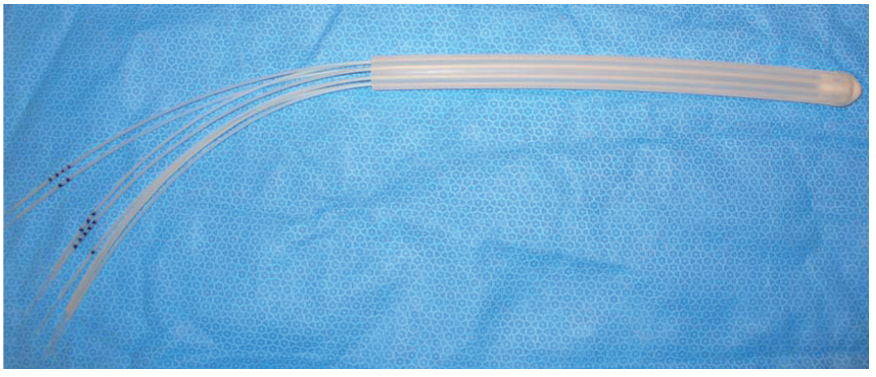


Figure 2: Depicts the endorectal applicator (Oncosmart®, Nucletron, Veenendaal, the Netherlands) used to apply High Dose Rate Brachytherapy.

TREATMENT PLANNING

A CT-scan, with the unloaded applicator inserted, was performed for delineation and treatment planning purposes before the first HDRBT fraction. A 3D reconstruction of the applicator and radio-opaque endorectal clips was made and the target volume delineated on the CT-images. A 2D anterior-posterior projection of applicator and clips was reconstructed as a reference for C-arm fluoroscopy guided reinsertion of the applicator prior to each HDRBT session (week 9-11, Figure 3b).

DATA ANALYSES

We evaluated retention rates between the two clip types over three different observational periods (period 1: pre-HDRBT (week -2 - 8), period 2: during HDRBT (week 9-11) and period 3: post-HDRBT (week 12-16)) (Figure 1). The percentage and absolute number of clips still attached during follow-up endoscopy and on the fluoroscopic images were determined. To assess the retention rates of the two clip types (Quickclip or Resolution) a logistic mixed effects model was constructed with clip type as a fixed effect. To account for the influence of both the different periods (different in length and use of an endoluminal applicator) and the duration of attachment prior to assessment we included placement (beginning of period 1 or 2) and assessment period as fixed effects. The assessments of clip retention was assumed to be correlated when they relate to the same clip (assessed for different periods) or from clips within the same patient. To account for this cluster correlation we included clip and patient id as random intercepts. Due to insufficient events in period 2 a logistic model was unable to be constructed; hence the comparison of the retention rates of the two clip types in this period was performed using a Mantel-Haenszel test. Where appropriate, two-sided p-values are reported with a significance level set at 0.05.

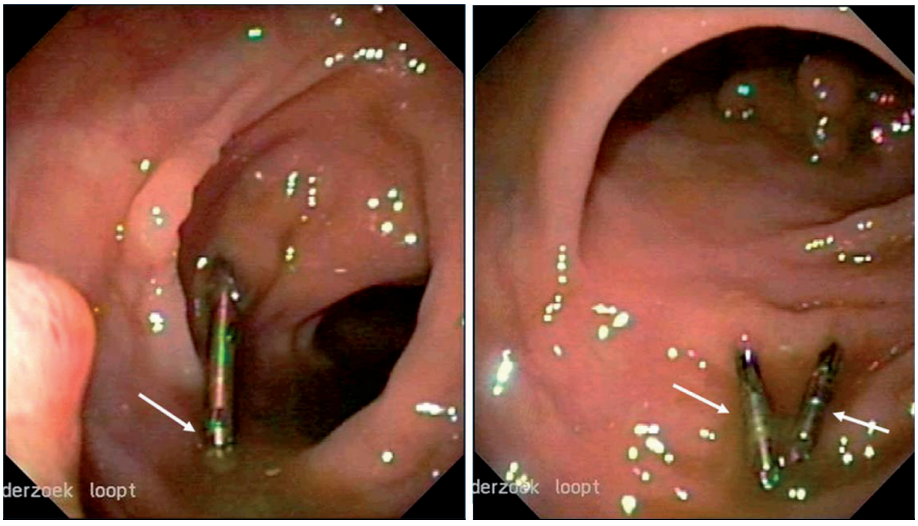
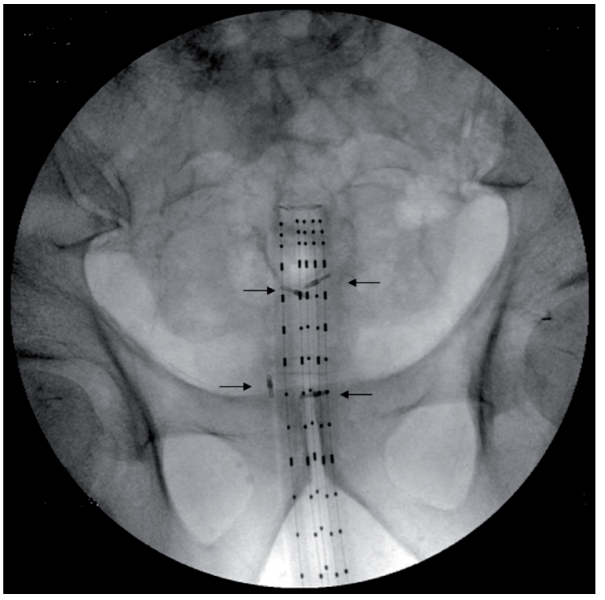


Figure 3 Imaging of the endoclips: A) Shows endoscopic images of an attached Resolution clip on the left (with a recognizable silver part at the loose end) and 2 attached Quickclips on the right (with a recognizable silver part at the centre of the clip).



B) Shows a fluoroscopic image as made for HDRBT planning purposes and in between HDRBT fractions. Four Quickclips are still attached (arrows).

RESULTS

Six male and three female patients were evaluated. Median age of patients was 81 (range 57-93) years. Seven of the nine patients completed the treatment. One patient did not receive HDRBT after the EBRT due to an ulcer located in the brachytherapy field, while the other patient not completing treatment died due to a non-treatment related cardiac arrest after the first HDRBT treatment. Retention rates for the different observational periods are depicted in Table 1.

In this study a total of 44 clips were placed during endoscopy, either at the beginning or at the end of period 1. At the beginning of period 1 (before EBRT), 26 clips were placed. The median duration of period 1 was 81 (49-90) days. Of the 20 Quickclips placed, 7 (35%) were visualized during the follow-up endoscopy at the end of period 1. Four of the 6 (67%) Resolution clips placed were visualized at this second endoscopy. During the same endoscopy at the end of period 1, 18 clips were additionally placed (15 Quickclips and 3 Resolution clips) to replace dislodged clips. Median time between placement/visualization at the end of period 1 and the next follow-up endoscopy (end of period 3) was 72 (range 33-91) days. No Quickclips survived all three periods, while 1 additionally placed Quickclip was visualized at the end of period 3. One of the 6 Resolution clips placed at the beginning of period 1 survived all three periods and was still visible at last follow-up after 231 days. One of the 3 additionally placed Resolution clips was visualized at the end of period 3 as well. Therefore, at the follow-up endoscopy after HDBRT (end of period 3), 1 (7%) Quickclip and 2 (40%) Resolution clips were visualized.

Table 1: Clip retention rates over three periods.

Period	Period 1		Period 2						Period 3	
Evaluation	During 2nd endoscopy (Before HDRBT, after EBRT)		Images after week 1 (During HDRBT)		Images after week 2 (During HDRBT)		Images after week 3 (During HDRBT)		During 3rd endoscopy (After HDRBT)	
Patient	Quickclip (visualized/ placed[a])	Resolution (visualized/ placed[a])	Quickclip (visualized/ placed[b])	Resolution (visualized/ placed[b])	Quickclip (visualized/ placed[b])	Resolution (visualized/ placed[b])	Quickclip (visualized/ placed[b])	Resolution (visualized/ placed[b])	Quickclip (visualized/ placed[c])	Resolution (visualized/ placed[c])
1	0/1	0	2/5	0	1/5	0	1/5	0	0/1	0
2	4/11	0	7/7	0	6/7	0	6/7	0	0/6	0
3	0	0	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
4	2/2	1/1	2/2	0/1	2/2	0/1	2/2	0/1	0/2	0
5	0/1	0/1	no images	no images	no images	no images	no images	no images	0/2	0/1
6	0/1	1/1	2/2	1/1	2/2	1/1	2/2	1/1	0/2	0/1
7	0	1/1	0	1/1[d]	-	-	-	-	-	-
8	0/2	0/1	1/1	1/1	0/1	1/1	no images	no images	0	0/1
9	1/2	1/1	½	1/1	0/2	1/1	0/2	1/1	0	1/1
Total	7/20 (35%)	4/6 (67%)	16/20[e] (80%)	5/6[e] (83%)	12/20 (60%)	4/5 (80%)	12/19 (63%)	3/4 (75%)	1/14 (7%)	2/5 (40%)

Superscripts: a: "Placed" includes those clips placed during the first endoscopy. b: "Placed" includes those clips that were placed at the 2nd endoscopy but also those (7 Quickclips and 4 Resolution) that were still attached from the 1st endoscopy. c: "Placed" are the number of clips at last visualization in period 2 (for patient 5 this is during placement during period 2). d: This patient died due to a sudden cardiac arrest during the HDRBT. e: Due to missing images of patient 5, the 2 placed Quickclips and 1 resolution clip were excluded from the analysis in the corresponding period. Abbreviations: EBRT: external beam radiotherapy, HDRBT: high dose rate brachytherapy.

Retention rates gathered from the fluoroscopy images, acquired every week during the HDBRT, are depicted in Table 1. After 1, 2 and 3 weeks, these were 80%, 60% and 63% for the Quickclips versus 83%, 80% and 75% for the Resolution clip. In case no image was available, the clip was censored which explains why the 3 week Quickclip retention rate is higher than the 2 week rate. The retention rates after 1, 2 and 3 weeks in period 2 did not differ significantly between the 2 types of clips (p=0.17, Mantel Haenszel test). The Resolution clip had a higher overall retention rate than the Quickclip [Odds Ratio: 96 (2.5-3614), p=0.01]. In comparison to the first period, long-term retention rates deteriorated significantly in the third period when the endoluminal applicator had been inserted [Odds Ratio: 0.01 (0.0003-0.2), p=0.003].

DISCUSSION

In this study, we found the Resolution clip to be superior to the Quickclip in situations where long-term attachment is warranted. The Resolution clip remained attached longer than the Quickclip, with encouraging long-term retention rates of up to 67% for the Resolution clip after nearly 12 weeks. In contrast, only 35% of the Quickclips remained attached.

Recently, Eun Ji Shin *et al* compared the attachment duration of two endoscopic clips (the Quickclip's predecessor, the HX-5L, versus the Resolution clip) in the gastric mucosa of 5 pigs. They also found that the Resolution clip had the longest rate of retention, being visualized during follow-up endoscopy after 1, 2 and 4 or 5 weeks (range of retention rates: 4-5 weeks) and concluded that it be preferred over the HX-5L clip (80% dislodged within 2 weeks) when long-term attachment is important[171]. Similar results were reported in a randomized controlled study of 3 types of endoscopic clips used for haemostasis in bleeding gastric ulcers in 7 canines. In their study, the median clip retention time was 2 weeks for the Quickclip (maximum duration of attachment of 3 weeks) and 4 weeks for the Resolution clip (maximum duration of attachment of 18 weeks)[172]. The nature of our study enabled the first report in humans in vivo and is in line with these reports, favouring the Resolution clip when long-term attachment is required. Furthermore, we describe retention after almost 12 weeks follow-up. Long-term attachment of an endoscopic clip was first described in 1994 when Iida *et al* reported clip retention (HX-3L, Olympus, total number of clips placed unknown) of up to 26 months after placement in a patient during a colonoscopic polypectomy[173]. In our study, 1 Resolution clip was even visualized 33 weeks after placement, while the longest measured attachment of a Quickclip was 15 weeks. Clinical indications that would benefit from long-term attachment include the fixation of stents and feeding tubes in the oesophagus and bowel, respectively.

Regarding the effect of mechanical exertion on the endoscopic clips, we found the following: overall, the resolution clip survived the continuous passing of stools more effectively than the Quickclip. However, in our study, the retention rates of both the Resolution clip and the Quickclip deteriorated during the second and third period (during and after HDRBT) in comparison to the first period, where patients underwent external beam radiotherapy (Table 1). As suggested earlier, one probable cause for this decreased retention is the fact that an endorectal brachytherapy applicator was placed in the

second period in order to plan and perform the HDBRT (4 times in total), which could have mechanically dislodged both types of clips in the process. Another plausible reason could be that some of the clips (7 Quickclips and 4 Resolution clips) evaluated in period 2 were placed during the first endoscopy. With a grip that theoretically deteriorates due to cell renewal and mechanical pressure of passing stools during defecation, these clips could possibly have been on the verge of dislodgement, leading to the decreased retention rate over periods 2 and 3. Regarding the subgroup of endoscopic clips in our study in which attachment was determined after 1, 2 and 3 weeks, retentions rates (Table 1) are at least in line with those reported in the abovementioned study by Jensen *et al* (Quickclip: 74%, 30% and 11% versus the Resolution clip: 65%, 58% and 45% after 1,2 and 4 weeks)[172]. Interestingly, when one only looks at the retention of the two clip types during these periods (at 1,2 and 3 weeks) in our study the Quickclip retention rate did not significantly differ from that of the Resolution clip (p=0.17). That in contrast to what Jensen *et al* describes, although this could be due to a lack of power for this sub-group analysis in our study. Our result implies that short-term attachment directly after external mechanical exertion (endorectal applicator) is not significantly superior for the Resolution clip, but that does seem to be the case in the period thereafter in which 40% of Resolution clips were visualized, versus 7% of the Quickclips. This suggests that if the clip survives the applicator, the Resolution clip seems to survive longer.

Finally, we found the endoscopic clips to be useful in locating and marking the tumour borders for radiotherapy volume delineation and for optimizing the position of the endorectal brachytherapy applicator. Pfau *et al*[48] recently reported similar promising results in optimizing radiotherapy volume delineation in oesophageal cancer patients. However, a possible downside for the clinical use of endoclips is the fact that they are not MRI-compatible, having caused artefacts on MRI in our series.

In conclusion, in this small prospective study we evaluated long-term attachment of the Quickclip and the Resolution clip to human rectal mucosa. We found that up to two thirds of Resolution clips were visualized at follow up after a median of nearly 12 weeks illustrating their superior value in situations where long term attachment is warranted.

CHAPTER 7

Quantitative intra-operative assessment of peritoneal carcinomatosis - a comparison of three prognostic tools

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ABSTRACT

BACKGROUND

Selecting patients for cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy (HIPEC) remains challenging. We compared the predictive power of three intra-operative assessment tools of peritoneal involvement of colorectal cancer.

METHODS

Ninety-two procedures (1999-2005) were prospectively scored using the Simplified Peritoneal Cancer Index (SPCI) and 7 Region Count. The Peritoneal Cancer Index (PCI) was retrospectively scored using the SPCI tool, operative notes and pathological reports. Endpoints were completeness of cytoreduction and overall survival. Logistic regression and Receiver Operating Characteristic (ROC) curves were applied to compare the predictive value of the three scoring systems on completeness of cytoreduction.

RESULTS

After a median follow-up of 31 months, the median overall survival was 25.6 months. It decreased to 7.3 months, when cytoreduction was incomplete ($p = 0.001$). An increased PCI, SPCI or number of regions were all associated with a decrease in probability of complete cytoreduction ($p < 0.05$). With complete cytoreduction as outcome, the ROC areas for the PCI, SPCI and 7 Region Count were 0.92, 0.94 and 0.90, respectively ($p = 0.14$). Using a cut-off value of 16 in the PCI system ($p = 0.03$), 13 in the SPCI system ($p = 0.04$) and 6 regions in the 7 Region Count ($p = 0.0002$) the probability of complete cytoreduction decreased significantly.

CONCLUSION

The PCI, SPCI and 7 Region Count are useful and equally effective prognostic tools predicting completeness of cytoreduction and associated improved survival. The 7 Region Count may be preferred due to its practical simplicity.

INTRODUCTION

Peritoneal carcinomatosis (PC) is a manifestation of colorectal cancer being present in roughly 10% of patients at time of initial diagnosis and in approximately 25% of patients with recurrent disease[174-176]. The natural history of PC is associated with a median survival of approximately 6 months[177;178]. A prospective randomised phase III study[86] and a multi-institutional study[179] have both demonstrated that cytoreductive surgery followed by Hyperthermic Intra-PEritoneal Chemotherapy (HIPEC) improves survival in patients with peritoneal carcinomatosis of colorectal origin. These results have encouraged many surgical teams worldwide to embark on this relatively new treatment modality. Several studies show that HIPEC only works in patients who have undergone complete cytoreduction[86;180]. Long-term survival only seems to be reserved for this subset of patients, as reported in the long-term results of the abovementioned randomized controlled trial. After a median follow up of almost 8 years we found a 5-year survival of 45% in this subset of patients[181].

Patient selection is crucial to restrict this complex and potentially toxic treatment to patients in who complete cytoreduction is feasible. Cytoreductive surgery combined with HIPEC is associated with high costs, a treatment related morbidity of 27-35% and a mortality of 1.5-5%[182-184]. Furthermore, early disease progression has been observed in up to 30% of patients[182].

Consensus has been reached regarding pre-operative selection criteria. Patients with signs of extra-abdominal disease, with inoperable intra-abdominal disease, or with poor performance status are generally excluded from this extensive treatment. However, the low sensitivity of CT[185;186] or MR imaging of PC, especially when tumour deposits are smaller than 1cm, makes pre-operative selection difficult and inaccurate. Exploratory laparotomy is often the only way to reliably assess and select patients.

At present, five quantitative intra-operative abdominal assessment tools have been described for this treatment modality: Gilly Staging[187], Japanese Gastric Cancer P score[188], Peritoneal Cancer Index (PCI)[189], Simplified Peritoneal Cancer Index (SPCI)[180] and the 7 Region Count[180]. Comparison between these prognostic tools with regards to their power to predict complete cytoreduction and long-term survival has yet not been attempted.

In this study, we compare 3 tools namely: the PCI, as introduced by Sugarbaker at the Washington Cancer Institute, the SPCI and the 7 Region Count, as used at Netherlands Cancer Institute, in a series of 92 patients with peritoneal carcinomatosis of colorectal origin treated at the Netherlands Cancer Institute between 1999 and 2005.

PATIENTS AND METHODS

SCORING TOOLS

The Peritoneal Cancer Index (PCI) was established at the Washington Cancer Institute by Sugarbaker[189] and combines cancer implant size with cancer distribution, throughout 13 abdominopelvic regions,

producing a quantitative score with a maximum of 39. Two transverse and two sagittal straight lines, together with a division of the small bowel, artificially divide the abdomen into 13 regions. Each region is defined by the anatomic structures situated in that region. Figure 1 describes how lesion size and distribution are scored.

The Simplified Peritoneal Cancer Index[180] (SPCI) was established in the Netherlands Cancer Institute. The SPCI, like the PCI, calculates the tumour load, incorporating the tumour thickness with extent of peritoneal dissemination. However, the abdomen is, for practical convenience, divided into 7 anatomical regions. Each region incorporates certain anatomical structures and scoring is based on the visualized maximum thickness of tumour nodules in each region. The SPCI adds up to a maximum score of 21 (Figure 1).

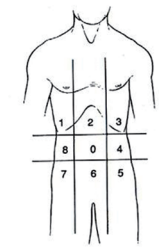
The more user friendly 7 Region Count[180] (Figure 1) was introduced by the Netherlands Cancer Institute following the SPCI and solely describes the number of affected regions out of 7 in the SPCI system, regardless of the tumour volume. Since 2002, 6 or 7 affected regions has served as a contra-indication for the combined modality treatment in the Netherlands Cancer Institute.

DATA COLLECTION

Ninety-two patients with peritoneal carcinomatosis of colorectal origin were treated by cytoreductive surgery and intra-operative HIPEC, between 1999 and 2005, at the Netherlands Cancer Institute. Procedures were performed as described by our group previously[184]. Patients with pseudomyxoma peritonei or other malignancies were not included.

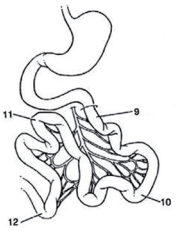
During laparotomy, involvement of 7 peritoneal regions, as well as tumour nodule size per region was prospectively recorded using the SPCI registration form[190]. With the help of operative notes and pathological reports, procedures were subsequently retrospectively scored using the PCI scoring system. In cases where information on regions and/or tumour load was incomplete, missing data were translated from the SPCI scoring sheet to the PCI scoring sheet. The PCI lesion size (LS) groups differ in magnitude from the SPCI groups (Table 1). LS-0, -2 and -3 are convertible from SPCI to PCI. However, when directly converting the LS-1 score from the SPCI score (<2 cm) to the PCI score (<0.5 cm) lesions measuring 0.5-2 cm in the PCI tool would be underscored (1 instead of 2). We corrected for this underscored PCI group 0.5-2 cm by allocating 1.5 instead of 1 point to the PCI group LS-1. When tumour location in the small bowel was in conclusive it was scored as follows: the distal ileum was scored when only isolated lesions were recorded which did not require partial bowel resection. The proximal and distal ilea were scored when the small bowel mesentery was involved or when partial resection was recorded. The distal jejunum was added to the combination when multiple small bowel resections were recorded and all four regions were scored when extensive small bowel infiltration was recorded to have created a surgical dilemma.

A



Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____
PCI	☐

Lesion Size Score
LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



B

Tumour Size	None	<2cm	2-5cm	>5cm
Score	0	1	2	3
Pelvis				
Right Lower Abdomen				
Omentum/Transverse Colon				
Small Bowel/ Mesentery				
Subhepatic Space/ Stomach				
Right Subphrenic Space				
Left Subphrenic Space				

C

Regions	Affected: yes/no
Pelvis	
Right Lower Abdomen	
Omentum/Transverse Colon	
Small Bowel/ Mesentery	
Subhepatic Space/ Stomach	
Right Subphrenic Space	
Left Subphrenic Space	

Figure 1: The 3 prognostic tools: Peritoneal Cancer Index (PCI)*, Simplified Peritoneal Cancer Index (SPCI) and 7 Region Count. * with permission from P. Sugarbaker.

Table 1: Scoring of the lesion size

Lesion Size (LS)		
Lesion Size Score	PCI	SPCI
0	None	None
1*	< 0.5 cm	<2 cm
2	0.5-5 cm	2-5 cm
3	>5 cm	>5 cm
Total Maximum Score (regions × LS)	39 (13 × 3)	21 (7 × 3)

** to correct for an underscored PCI group 0.5-2 cm, score=1 in the SPCI was scored as 1.5 in the PCI group. For example, a tumour nodule sized 1,3 cm was scored 1 point in the SPCI system and 1,5 in the PCI system. It would have received 1 without this correction and 2 if it was prospectively scored using the PCI system.*

Completeness of cytoreduction was recorded as follows; R1: no macroscopic residual tumour, R2a: residual tumour ≤ 2.5 mm and R2b: residual tumour > 2.5 mm. Complete cytoreduction was defined as a R1 or R2a result in this study.

STATISTICAL ANALYSIS

Logistic regression and Receiver Operating Characteristic (ROC) curves were applied to compare the predictive value of the 3 scoring systems on completeness of cytoreduction, e.g. R1 or R2a and R2b. Statistical level of significance in predicting complete cytoreduction was set at p=0.050. Overall survival was calculated from date of HIPEC procedure until date of death or date of last follow-up. Progression free survival was calculated from date of HIPEC procedure until date of progression or recurrence, date of death or date of last follow-up. Overall and progression free survival were investigated by a Cox regression. A uni- and multivariate analysis was performed for the following factors: gender, affected region, number of affected regions, result of cytoreduction, SPCI score and PCI score.

RESULTS

QUANTITATIVE ASSESSMENT ANALYSIS

Ninety-two procedures were performed and analysed in 49 women and 43 men. The median follow-up was 31 months (range 0-67). The median PCI score was 8.8 (range 0-26) and the median SPCI score was 6 (range 0-18). The mean number of affected regions was 3.8 of the 7 regions while in 20 patients more than 5 of the 7 regions were affected. The mean number of affected regions in the PCI system

was 5 of the 13. In 58 patients a recurrence or progression developed. Forty-five patients died of which 42 due to disease and 3 due to complications.

Results of the PCI system showed that the pelvis was the most affected region (80 of the 92 patients), followed by the central abdomen affected in 72 patients and the lower ileum affected in 65 patients. Volume of tumour was also found to be the greatest in the pelvis region followed by the central abdomen with a lesion size of >5 cm in 24 and 14 patients, respectively. In the 7 regions used in the SPCI and the 7 Region Count similar results were noted in the pelvis and omentum/ tranverse colon regions. The least affected regions in the PCI system were the lower jejunum (7 patients) followed by the upper jejunum together with the left flank, both affected in 8 patients. In the SPCI/ 7 Region Count the left subphrenic space was least affected (16 patients).

After cytoreductive surgery, no residual tumour (R-1) was left in 58 patients while in 26 patients residual tumour deposits measured less than 2.5 mm (R-2a). In 8 patients the cytoreduction was grossly incomplete (R-2b). In the latter group the PCI score ranged between 13-21 with a median of 18 while the SPCI score ranged between 10-18 with a median of 12. The median number of affected regions in this group was 6.5 of the 7 regions.

LOGISTIC REGRESSION ON RESULT OF CYTOREDUCTION

In the univariate analysis, both an increased PCI and SPCI, as well as an increased number of affected regions, were significantly associated ($p<0.05$) with a decrease in probability of complete cytoreduction (Figure 2). Using, in the literature described, cut-off values of <16 in the PCI system ($p=0.0002$), <13 in the SPCI system ($p=0.0011$) and <6 regions in the 7 Region Count ($p=0.0018$) the probability of complete cytoreduction decreased significantly when the cut-off was exceeded, as shown in Table 2.

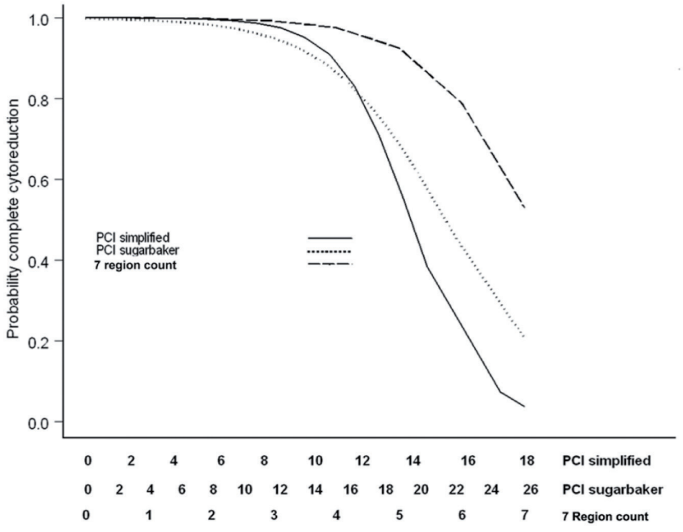


Figure 2: Estimated probability of complete cytoreduction using the PCI, SPCI and the 7 Region count

Figure 3 shows the ROC curves for the three prognostic tools. The ROC areas for the PCI, SPCI and 7 Region Count tools were 0.92 (95% CI 0.84-0.98), 0.94 (95% CI 0.89-0.99) and 0.90 (95% CI 0.83-0.97), respectively. By nearing the maximum value of 1, these estimates of the ROC areas indicate that all three prognostic tools are highly accurate in predicting a complete cytoreduction result. The difference between the three was not significant (p=0.14), suggesting that the three systems are similar.

SURVIVAL ANALYSIS

The median overall survival was 25.6 months (95%CI 20.9 - 29.4), with a median progression free survival of 13.6 months (95%CI 11.2-16.4). The overall survival decreased from 26.2 to 7.3 months when cytoreduction was incomplete (p=0.001, hazard ratio 3.9, 95%CI 1.7-8.8). In all three tools the quantitative scores were significant prognostic factors for overall survival, whereby a higher score/ number of affected regions correlated with a decreased survival. Using the cut-off values of <16 in the PCI system (p=0.03), <13 in the SPCI system (p=0.04) and <6 regions in the 7 Region Count (p=0.0002) the overall survival decreased significantly when the cut-off was exceeded, as shown in Table 2.

In univariate analysis, 3 of the 13 PCI regions [right upper (Hazard-Ratio 2.7), epigastrium (HR 3.9) and lower ileum (HR 2.3)] and 4 of the 7 SPCI regions [small bowel and mesentery (HR 2.5), right lower abdomen (HR 2), subhepatic space (HR 4.1) and left subphrenic area (HR 2.7)] were, when affected, significantly associated with decreased overall survival and progression free survival (except small bowel and mesentery).

In the multivariate analysis of affected regions and result of cytoreduction, the epigastric region (HR 3.3) in the PCI system and the subhepatic space (HR 2) in the SPCI system were independent significant prognostic factors for overall survival.

Table 2: Prognostic tools with associated probability of complete cytoreduction and overall survival

	PCI		SPCI		7 region count	
	<16	≥16	<13	≥13	0-5 regions	6-7 regions
Number of patients	82	10	83	9	72	20
Probability complete cytoreduction (95%CI)	96 (89.3-98.8)	50 (22.5 -77.5)	95 (87.9 -98.2)	56 (25.1 -82.3)	97 (89.6-99.3)	70 (47.2-85.9)
Median overall survival (95%CI)	25.6 (20.9-33.4)	11.3 (7.3-28.4)	25.6 (20.9-60.9)	20.9 (9.6-28.41)	27.7 (22.9-60.9)	12.6 (9.6 -22.5)

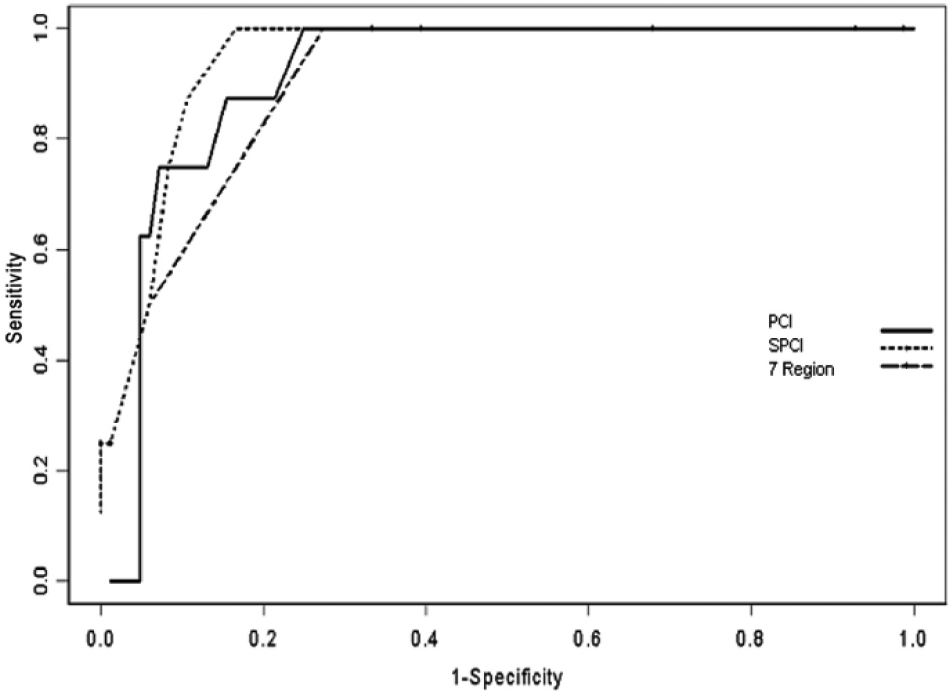


Figure 3: Receiver Operating Characteristic Curve

DISCUSSION

PRIME OBJECTIVE IS COMPLETE CYTOREDUCTION

The results of this study are in line with previous studies with regard to poor overall survival in patients in whom cytoreduction is incomplete. Prime objective in the selection of patients for this therapy must therefore be the probability to achieve complete cytoreduction. Our results show that the PCI, SPCI and the 7 Region Count scoring systems are equally effective in this respect. The 7 Region Count is, however, the easiest to implement, and may therefore has some advantage over the other systems.

CUT-OFF VALUES FOR THE PCI

The Washington Cancer Institute, pioneering the treatment modality, established the Peritoneal Cancer Index[189] and implemented it in the assessment of peritoneal involvement of sarcoma[191], mesothelioma[192], ovarian[193] and colorectal cancer[194]. Sugarbaker[194] reported that the 5-year survival of approximately 100 colon cancer patients was 50% with a PCI less than 10, 20% with a score of between 11-20 and 0% in those with a score of more than 20. They suggest a cut-off PCI of 20 above which the treatment should be abandoned and be replaced by palliative surgery. Elias and colleagues[195]

described that a PCI of less than 16 resulted in a significantly more favourable prognosis. In a series of 64 patients with peritoneal involvement of colorectal cancer they reported a 3 year survival of 60% versus 33% using this cut-off value. Our study confirmed these results whereby a PCI score < 16 was associated with a median survival of 25.6 months while it was 11.3 months for a score of 16 or more (p=0.03). Remarkably, there was no survival advantage of a PCI cut-off of >20 versus >16, as no patients in our study survived 30 months with a PCI of >16 or >20. The following critical comments regarding the PCI should, however, be addressed. Firstly, the numerous amount of 13 regions makes the tool tedious to implement. Secondly, the negative effect of small bowel involvement on prognosis is together with other crucial anatomical sites a well-known and important fact. However, the desired advantage by encompassing this fact (dividing the small bowel into 4 regions) is neutralized by the increased chance of an inaccurate overestimation of this region. The subjective and vague transitional point of the proximal and distal small bowel creates a possibility to under or overestimate tumour load and distribution. Resectable tumour nodules situated on transitions or if one small lesion is resectable on each of the four small bowel regions should leave the patient with sufficient functional small bowel but would receive a highly overestimated PCI.

CUT-OFF VALUES FOR THE SPCI AND 7 REGION COUNT

Our group[180] previously described important factors predicting poor outcome including poor differentiation, signet cell histological type and primary location of tumour in the rectum. Furthermore, no long-term survival has been achieved in patients where complete cytoreduction failed, acknowledging that complete cytoreduction is a basic necessity for a positive outcome[190]. We introduced a simplified version of the PCI scoring system to maximize simplicity and practicality and proved that it was useful in patients with colorectal cancer. Using the simple seven anatomic regions we observed that patients where more than 5 of the 7 regions are affected or with a SPCI greater than 12, the possibility of treatment benefit significantly diminished and was related to an increased rate of post-operative complications resulting in a higher morbidity and mortality rate[184]. We then went on to suggest that a SPCI of greater than 12 or 6-7 regions affected should serve as an intra-operative exclusion criterion. The results of this study confirm these previous reports. A SPCI score of lower than 13 was associated with a significantly increased overall survival (overall 25.6 versus 20.9 months, p=0.04) compared to patients with a higher SPCI. Furthermore, patients in whom up to 5 regions were affected had an overall survival of 27.7 months. This decreased drastically to 12.6 months when 6-7 regions were affected. A shortcoming of these two versions of the SPCI tool is the inadequacy to encompass the additional negative prognostic value of anatomical crucial sites.

OTHER SCORING SYSTEMS

The assumption underlying the PCI and SPCI is that tumour size, additional to tumour distribution predicts outcome. This is in line with the TNM system widely used in oncology and validated for many types of cancer, which shows that more cancer predicts poorer prognosis. So why does it seem to be different in peritoneal carcinomatosis of colorectal origin? A clue may be that many

of the high volume regions recorded in our patients were ovarian metastases, omental metastases and primaries or recurrences around the cecum. These tumour deposits usually are technically easy to resect. In this series, high volume disease in these areas did not adversely affect completeness of cytoreduction or survival. On the other hand, even small tumour deposits in the porta hepatis and around the pancreas are difficult to resect completely. This may explain why tumour deposits in these areas related significantly to poorer survival. It must also be emphasized that both PCI and SPCI are including both unilocular big masses and confluent multiple small deposits as high volume disease. It seems clear that these two categories of high volume disease represent a different tumour biology, and probably a different prognostic impact. In this respect Gilly probably has a point when he emphasizes the prognostic significance of the distinction between localized and diffuse presentation of PC. He introduced the Gilly Peritoneal Carcinomatosis Staging[187] which incorporates implant size (<5 mm, 5-20 mm, >20 mm) and distribution (localized or diffuse). It's efficacy was demonstrated in the EVOCAPE[178] study investigating the natural history of peritoneal involvement in patients with amongst others gastric, pancreatic, liver and colorectal cancer (n=118). The tool was also implemented in a study of 56 patients receiving the combined modality treatment[196]. The prognostic efficacy of the tool in the 26 colorectal cancer patients included in this study was, however, not reported. Unfortunately, a shortcoming of this simple prognostic tool is that the distribution is unspecific and incomplete in stages 3 and 4. The tool is inadequately capable of discriminating stages 2, 3 and 4. Stages 3 and 4 incorporate only the size of a lesion, without describing distribution. With the likelihood of cytoreduction being a chief prognostic indicator, a technically resectable solitary large tumour mass of 4 cm on the descending colon (stage 4) is related to a better prognosis than small nodules diffusely spread over the abdomen (grade 2). Finally, the Japanese[188] established and validated a relatively simple tool to assess peritoneal involvement of gastric malignancy. Patients are divided into 4 groups after exploration and cytological tests. To our knowledge, no reports have been made on the implementation of this tool in colorectal cancer patients. Because we studied patients with PC of colorectal origin in this series, we chose to exclude the latter two scoring systems in our study.

STUDY LIMITATIONS

Due to its design, this study has its limitations. Although the SPCI and the 7 Region Count were prospectively recorded and are probably accurate, the PCI was retrospectively assessed. This may have led to some underscoring, especially regarding tumour distribution and tumour size on the small bowel. Another weak point is the fact that from 2002 onwards, patients with 6 or 7 affected regions were excluded from the treatment causing a selection bias in our study population. It is, however, difficult to foresee any new studies that will neglect the important lessons for selection that have been learnt the hard way during the past decade, both by our group and others. A prospectively designed study would more accurately be able to compare the scoring systems. A large disadvantage, however, is that it would take numerous years before survival analysis can be done and conclusions are made.

CONCLUSION

Notwithstanding this, the message from this study is clear: Intra-operative selection for cytoreduction and HIPEC in patients with peritoneal involvement of colorectal cancer should be based on early assessment of the extent of the peritoneal deposits. A PCI ≥ 16, a SPCI ≥13 and a 7 Region Count >5 are indications to abort the attempt to complete cytoreduction and scale back to palliative approaches. These three staging tools are equal in their accuracy.

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CHAPTER 8

Discussion and future perspectives

DISCUSSION AND FUTURE PERSPECTIVES

EVOLVING TREATMENT MODALITIES IN RECTAL CANCER

Patients who undergo curative rectal surgery are at risk for local or distant disease recurrence. Local recurrence within the pelvis is especially feared since this outcome is often unresectable and patients, as a result, can suffer a slow, painful death. Over the last few decades treatment of rectal cancer has evolved immensely resulting in local recurrence rates after 5 years dropping from 20%-38%[24;197] to approximately 5-10%[18;19;198], while overall survival after 5 years has increased from 50% to 65%[24;198]. The most important risk factor for local recurrence is a positive circumferential resection margin(CRM)[68]. CRM involvement is also associated with poor distant control and decreased overall survival[68;70]. Therefore, attaining a negative CRM has become one of the primary goals in the treatment of rectal cancer.

Improvements started with the introduction of a different surgical approach[69], the so-called total mesorectal excision (TME), which consists of sharp dissection under direct vision along the mesorectal fascia. Simultaneously, neoadjuvant short-course radiotherapy (SCRT 5x5 Gy) was introduced[24;199] originally to compensate for poor local control after conventional surgery but later also proved to be effective in optimizing local control in resectable rectal cancer treated with TME surgery[20]. However, those with positive margins after preoperative SCRT and TME remain at significant risk for local recurrence. Patients with locally advanced rectal cancer (LARC) receive chemoradiotherapy (CRT) consisting of long-course preoperative RT with the addition of concomitant chemotherapy followed by a longer delay to surgery to allow for downsizing and downstaging of the tumour. Subsequently, local control in this subgroup with LARC has improved[4;29;30;96]. In the recent randomized (C)RT and TME trials these improvements in local control have surprisingly not translated into prolonged overall survival, possibly due to an increase in other unknown causes of death. Moreover, rectal cancer surgery (including TME) is associated with significant adverse effects with regards to long-term organ dysfunction and sexual dysfunction, and RT adds significant acute and long-term toxicity[59-61;200]. To maximise patient benefit these adverse effects need to be continuously weighed up against the numbers needed to treat to prevent a local recurrence.

Meanwhile, with the introduction of the MRI, imaging has improved preoperative staging thereby facilitating a more patient-tailored approach[12]. Two radiological studies[11;94] demonstrated that MRI can accurately predict involvement of the surgical CRM, thereby shifting the importance of an accurate T-stage on MRI to the more clinically appealing mesorectal fascia (MRF) at risk for a positive CRM after TME. With the MRI, tumours can nowadays be stratified according to the risk of a positive CRM, and treated accordingly.

One of the most important factors governing prognosis in cancer is the presence of lymph node metastases[201], which explains its inclusion in the TNM cancer classification system. Prior to surgery, the presence of positive mesorectal lymph nodes is indicative for the need of preoperative (C)RT. As yet, no pathognomonic criteria are known to diagnose affected lymph nodes, however size above 1 cm is

very convincing with 93% being positive[202]. A more in-depth understanding of the morphology of these pathologic lymph nodes will increase staging accuracy. For instance, size, inhomogeneity and border contour seem to be predictive factors that increase risk of involvement[13]. Promising results of special contrast agents, like gadofosveset, used to enhance and distinguish pathologic from benign lymph nodes have been reported but not yet implemented in clinical practice[203]. Unfortunately, the current available clinical staging modalities remain unreliable in detecting positive lymph nodes smaller than 1 cm. Our results on accuracy of N-staging in those not undergoing CRT (whereby no downstaging is expected) demonstrate under- or over-staging of nodal disease in up to 37% of patients *(Chapter 2)*.

As a consequence of the introduction and refinement of these different treatment strategies, the treatment of rectal cancer has become a complex and multidisciplinary team effort. The multidisciplinary team (MDT) discussion plays an important role in preoperative stratification and also serves as a platform for decision making, for example to decide to deviate from evidence-based guidelines. A population-based study demonstrated the positive effect of an MDT by reporting a decrease in the positive CRM rate after the introduction of a MRI-based MDT discussion for all patients[3]. In our regional audit we demonstrated that in only half of patients documented discussion in a MDT took place *(Chapter 2)*. Reasons for not discussing the patient or not documenting decisions would be interesting to know and could include practical problems, but also non-compliance by specialists not aware of the potential benefits. Ten per cent of patients receiving SCRT or no RT ended up with a positive CRM, indicating more advanced disease and the need for preoperative CRT. Improving the quality of the MDT and increasing the number of patients being discussed may perhaps lead to a decrease in unnecessary positive CRMs although an inadequate surgical technique, resulting in an incomplete TME specimen, may also lead to (unnecessary) positive CRMs. This emphasizes the importance of quality of surgery but also the feedback from the pathologist. Regarding pathology, our audit revealed that the CRM itself is underreported in the histopathological report. These results together emphasize the importance of quality assurance through audits of region- or nationwide treatment results, outside of randomized controlled trials, and also indicate the difficulty of translating the results gained in large trials to daily practice.

A way to assure quality of care on a population level is to introduce evidence-based guidelines, standardize treatment according to risk stratification and close the loop of care with an audit which in turn generates hypotheses for further prospective research. Once proven in prospective studies, new evidence also needs to be properly embedded in common practice through workshops and uptake in the guidelines. In order to be able to assess the quality of care, both process and outcome indicators must be assessed and observed over time. In 2009, a national initiative arose to improve quality of care and the Dutch Institute for Clinical Auditing (DICA) was established. Under auspices of the DICA, the Dutch Surgical Colorectal Audit (DSCA) forms a prospective case-mix adjusted audit with feedback on quality of care as compared to the median. This has amongst others led to a rise of rectal cancer patients being discussed in a MDT from 80% in 2009 to 96% in 2011, and to stricter compliance to national guidelines[89]. With a database coverage of 94% of all diagnosed rectal tumours in the Netherlands in 2011, valuable information is being gathered which will facilitate benchmarking

and continuous evaluation of quality of care over time, be an incentive to the MDTs to improve quality of care and make analyses possible to optimize cost-effectiveness.

SURGERY

QUALITY OF SURGERY

The paradigm "a surgeon has only one chance to cure the disease" is, due to the nature of the disease and its location deep within the bony pelvis, highly applicable to rectal cancer. Complete surgical resection using the TME technique, has led to improved local control and at present remains the cornerstone in the treatment of rectal cancer[19;69;204]. However, quality of TME varies and may result in differences in outcome[92;93;205]. A positive CRM after surgery can be caused by various factors, the most important of which being suboptimal quality of surgery, aggressive and progressive tumour growth, therapy resistance but also preoperative under-staging. Following the introduction of TME on a national level further steps have been made to decrease the rate of positive CRMs. More attention has been paid to the plane of surgery, which can be assessed by evaluating the macroscopic completeness of the specimen. The plane of surgery correlates with both local recurrence and overall survival[92] and deserves to be assessed and reported routinely. A more in-depth analysis of the TME study[205] and following pooled analysis[206] of the randomized controlled trials showed that an APR in itself is a significant predictor of CRM involvement and subsequent local recurrence. In the distal rectum the mesorectum steadily narrows down at the level of levator muscles and this understanding has led to a change in surgical approach for distal rectal cancer by maintaining a "cylindrical" resection distal from the levator muscles to retain adequate circumferential margins. This more extensive extra-levator approach, which pays more attention to the perineal phase and sometimes includes direct muscle flap reconstruction techniques, has led to decreased CRM involvement at a cost of more perineal wound complications[159-162]. We confirmed this, with more perineal wound complications occurring in those requiring more extensive resections *(Chapter 4)*. Finding a balance between oncologic safety and acceptable toxicity is vital, as possible downsides of more extensive surgery in locally advanced rectal cancer, in general, are an increased risk of surgical morbidity and mortality.

SURGICAL MORBIDITY

Surgical morbidity is a serious problem in rectal cancer surgery significantly affecting quality of life. To ensure uniform documentation and enable inter-institutional comparison, strict definitions of complications are however required. Regarding the definition of anastomotic leakage and perineal wound complications, it is remarkable how the reported definitions vary in the reviewed phase II studies[123;125;126] and European randomized trials[4;30;52;56;60;90;96;117;137] in rectal cancer. The scope of a definition and the way it is implemented largely determines the reported complication rate. It is comprehensible that surgical complications are underreported when they are not well defined or do not form the primary endpoint of a (large) multicentre study. In our series we used strict definitions

and classified complications according to the modified Clavien-Dindo classification[134;135] which has been validated to score surgical complications *(Chapter 4)*.

In roughly 25% of patients the sphincter will be resected leaving a permanent colostomy. After TME only, almost 40% of patients in which the sphincter is saved will develop faecal incontinence[61]. Sexual dysfunction is also a common complication[59] after TME indicating the different adverse effects of surgery on the pelvic anatomy. In LARC where surgery is often more extensive, we found that acute surgical morbidity following CRT is profound with 27% of LAR patients developing an anastomotic leakage, while after an APR perineal wound complications occurred in 37% of patients. Furthermore, 20% of patients were re-admitted to hospital within 30 days after discharge, underlining the importance of thorough follow-up. Fortunately, surgical morbidity did not translate into mortality; however, long-term functional results and quality of life were not evaluated in this series.

Decreasing surgical morbidity is another aim of the recently initiated DSCA. By prospectively registering postoperative complications, rates thereof have now been benchmarked. Furthermore, the database can be implemented to identify predictive factors and identify and treat complications earlier on. A decrease in the relative risk of 14% for developing major complications was realized over the period 2009 to 2011, whereby a major complication was defined as an event causing death, requiring a re-intervention or causing hospital admission longer than two weeks[89]. Recently, guidelines have called for centralisation of LARC and locally recurrent rectal cancer treatment to further increase quality of complex surgery required across different anatomical compartments in the pelvis, but also to optimize multidisciplinary post-operative care.

NEOADJUVANT TREATMENT

CONTINUE TO INCREASE RESPONSE IN LARC

Neoadjuvant (C)RT has firmly established itself as an important therapy becoming more effective over the years. The favourable results with regards to local control and tolerable toxicity after the addition of chemotherapy to long-course radiotherapy have been demonstrated in randomized trials in LARC[4;29;96]. Furthermore, preoperative CRT resulted in significantly more downsizing, downstaging and more pathologic complete responders in comparison to RT alone[28]. At present, combinations of chemotherapy concomitant to RT give more toxicity without oncologic benefit compared to single 5-FU-based CRT[145], except one randomized trial presently awaiting mature follow-up but already demonstrating more complete responders (17% versus 13%) after adding oxaliplatin to the 5FU-based CRT regimen[207]. An important next step would be to increase response rates to decrease CRM involvement rates of 16% in LARC *(Chapter 5)*. Theoretically, short-course RT (5x5 Gy) and long-course RT (25x2 Gy) have a similar biological effective dose raising the question which is clinically superior. Only the latter presently includes a delay to surgery thereby allowing downstaging and downsizing. Recently, two studies have compared SCRT with direct TME and CRT followed by delay[31;32]. As expected, more downstaging was observed after CRT but no significant difference with regards

to local/distant recurrence or overall survival was found. However, the studies were underpowered for these endpoints, thereby limiting firm conclusions. The Stockholm III trial which has recently completed accrual is investigating the effect of different delays to surgery. Patients with resectable rectal cancer are randomized to SCRT (5x5 Gy) followed by surgery within one week or after 4-8 weeks or long-course RT (25x2 Gy) followed by surgery after 4-8 weeks. Participating hospitals were allowed to choose to randomize between 2 or 3 groups, and individualize this per patient which may introduce the risk of selection bias. Interim analyses on acute toxicity and surgical complications show no significant differences in the 3 arms[208]. It appears that post-operative stage was more favourable in the delayed surgery groups with no residual tumour found in 0.5% (5x5 Gy with direct surgery), 12.5% (5x5 Gy with delayed surgery) and 5% (25x2 Gy with delayed surgery), indicative of downstaging. These interim results are in line with retrospective series reporting downstaging after SCRT and delayed surgery in patients medically unfit for CRT[144;209]. Hopefully the Stockholm III study will provide the answer whether SCRT followed by delayed surgery will match the response of long-course RT and delayed surgery. The delay may open up logistical opportunities to add systemic chemotherapy to eradicate micrometastases and possibly increase distant control and OS.

Another promising option, implementing induction systemic chemotherapy followed by CRT and TME, demonstrated high complete and near complete response rates, again with considerable toxicity, in non-resectable rectal cancer patients in a British trial[210]. One study investigated dose escalation and addition of a platinum derivative by comparing treatment with 45 Gy radiotherapy in 25 fractions with concurrent capecitabine versus 50 Gy radiotherapy in 25 fractions with capecitabine and oxaliplatin, but reported no benefit with regards to complete response rates, LR, distant metastases or OS[33;211]. With regards to radiotherapeutic options to increase downstaging and downsizing, several studies have reported a dose-response relationship[99;212-214] indicating that dose escalation, for instance, with a boost delivered with contact therapy, endorectal brachytherapy or during IMRT is clinically appealing. Results on the addition of biologicals targeting molecular markers, for instance vascular endothelial growth factor specific antibodies like bevacizumab[215] or epidermal growth factor receptor antibodies like cetuximab[216-219], as part of the CRT have been disappointing with regards to increased efficacy.

LESS NEOADJUVANT THERAPY WITH ADEQUATE TME IN LOW RISK PATIENTS?

In subgroup analyses of the MRC-CR07 and the Dutch TME studies, LR rates doubled if no SCRT was used prior to TME in TNM stage III rectal cancer, thereby firmly establishing the absolute need of preoperative RT for these patients[90;198]. Of note, despite a significant reduction in local recurrences in TNM stage I patients, the benefit from preoperative SCRT may be questioned as an absolute reduction of 2,6% for all eligible patients implies that 38 patients have to be irradiated to prevent one local recurrence. Furthermore, no significant benefit from preoperative SCRT could be demonstrated for stage II patients in this study[198]. In the MRC-CR07 study[90] the beneficial effect of RT was found in all stages of disease, but due to low incidence of recurrence in stage I and II the beneficial effect may not outweigh adverse effects, especially as no survival benefit was found. The concept of selectively treating patients with TME only was confirmed in a prospective multicentre trial[220] in dedicated

European centres which reported a LR rate of only 2.3% in TNM stage II rectal cancer (n=43), staged with MRI and treated with TME only. Therefore, in patients with TNM stage I or II disease high quality TME only is a valid treatment option.

LESS SURGERY AND MORE (C)RT?

Another important question is whether it is more beneficial to scale down aggressive surgical resection, to avoid morbidity and organ dysfunction, by implementing more effective neoadjuvant therapies? As preoperative CRT causes downstaging, less invasive surgical options have become more clinically appealing, especially in lower stage tumours. Promising results of (C)RT followed by local excision instead of TME in good responders with cT2-3 disease indicate the possibilities[221;222]. If the excised specimen contains residual disease or downstaging is insufficient, additional TME may follow. This is also the design of the phase II CARTS study, where the proposed accrual has been reached, and patients with cT1-3 N0 M0 distal rectal tumour cancer are treated with CRT followed by TEM if downstaging is observed[223]. Furthermore, the toxicity of this combination will be evaluated, with special attention for dehiscence of the TEM wound after CRT.

In the elderly population the concept of minimizing surgery related adverse effects is also actual as consequences of surgical complications are larger than in the middle-aged population and may even be lethal[62]. Definitive radiotherapeutic regimens, like external beam radiotherapy followed by endorectal brachytherapy, might gain ground in this fragile patient group[224]. Lastly, as more treatment options become available, patient information on advantages and disadvantages of treatment options as well as evidence-based quality of life will govern shared decision-making[225;226].

CAN WE WAIT AND SEE?

A pathologic complete response (pCR) diagnosed after preoperative CRT followed by delayed TME occurs in up to 30% of cases. These patients have been associated with an excellent outcome in numerous series[38;147]. Different factors play a role in determining the pCR rate. Firstly, rates of pCR are dependent on the extent of histopathological analysis, whereby thorough processing and sampling of deeper layers within the specimen in search for residual tumour cells may result in more accurate but lower pCR rates. Traditionally, surgery is performed approximately 6 weeks after completion of CRT to allow for response and patient recuperation from CRT-related toxicity. Emerging evidence suggests that the response to CRT is time-dependent, with more delay to surgery resulting in a higher rate of pCR[227-229]. Whether patients achieving a pCR after longer delays than 6-8 weeks also have the same favourable prognosis is unknown. Another factor affecting reported pCR rates is patient selection for CRT, as a cT2 tumour is obviously more likely to respond completely than a cT4 tumour. It is unclear whether the prognostic benefit of CRT induced regression is similar between less advanced and locally advanced tumours. However, the effect of pCR on long-term outcome was not affected by clinical T or N stage in a pooled analysis of pCR patients whereby response was assessed after 6-8 weeks after CRT[38].

The concept of a pCR after neoadjuvant therapy questions the need for additional resection and may be a solution to decrease the surgical morbidity. The group of Habr-Gama *et al* have published multiple series on a non-operative "wait and see" policy in those patients in whom no clinically detectable tumour is found after CRT[39]. They reported a locoregional failure rate of only 3% in a series[39] of distal rectal cancer patients (20% cT2, 70% cT3, 11% cT4 and 23% cN+), which is comparable to those with a pCR after resection. These results have been confirmed by another small single centre experience[40]. The long term oncological outcome following wait and see is however unknown. A key limitation of this policy resides in the inability to assess response accurately with present day imaging. *Chapter 5* adds knowledge to this option by demonstrating that CRT with capecitabine is an effective regimen resulting in a pCR rate of 20% in LARC with 39% T4 tumours. In this study, with central revision of the pathology, we however also demonstrate the potential risks involved in this group of patients. Counter intuitively, we demonstrated poor outcome in those with a near complete response and a significant percentage lymph node metastases in those with a pCR, underlining the risks of a wait and see policy. Furthermore, with the rectum being left in situ during this organ sparing approach the applied RT may perhaps lead to long-term toxicity.

RESPONSE PREDICTION

With regards to the assessment of response to neoadjuvant therapy itself, imaging will play an increasingly important role in the future as more interest is gained in organ sparing strategies and minimizing overtreatment in non-responders. At present it is difficult to distinguish (residual) fibrosis from tumour with the modalities at hand. Pathological analysis remains the gold standard, but functional imaging would be more practical in distinguishing responders from non-responders during the treatment itself. Diffusion-weighted MRI seems promising with responding tumours showing a higher apparent diffusion coefficient (ADC)[230]. However, further optimization and validation is required before this technique will reach clinical practice.

The use of another promising tool, the ^{18}FDG labelled PET, in combination with clinical variables, to predict pCR has been tested in a multicentre study[231] including sequential PET-CT imaging one week before and 6-8 weeks after CRT. The resulting nomogram performed with a sensitivity of 0.62 and a specificity of 0.88 in the validation series. Although the optimal time point of imaging needs to be refined, accurate PET-based prediction has been shown already after 2 weeks[232]. Interestingly, associations between preoperative ADC measurements and SUV measurements half way during and after CRT have been demonstrated (but not yet validated) to have a sensitivity for predicting a pCR of up to 100% and a specificity of 94%, suggesting a synergistic effect of combining these tools[233].

In conclusion, at present a wait and see policy seems to carry too many risks due to limitations in response assessment. In the future, knowledge gained on genetic profiles and using blood biomarkers will hopefully contribute to optimizing the specificity and sensitivity of response predicting models. Ideally, an accurate re-staging model using different tools (DW-MRI and ^{18}FDG-PET) could predict response early on in the neoadjuvant treatment, and could then be used to select patients to be

considered for less invasive surgical interventions or even a “wait and see” policy. On the other hand, based on the early predicted response, early modifications of the treatment protocol are possible, which in suboptimal responders could include dose escalation to improve response or necessitate direct extended surgery to prevent progression during neoadjuvant CRT.

IMPROVING RADIOTHERAPY TECHNIQUES TO DECREASE TOXICITY

The clinical target volume (CTV) in rectal cancer not only includes the rectum but also the surrounding mesorectal fat, containing possible microscopic tumour extensions and regional lymph nodes. As the irradiated volume increases more healthy tissue is inevitably and unnecessarily at risk. As reported in *Chapter 4*, grade 3 acute toxicity occurs in 21% during CRT for LARC, with diarrhoea and radiation induced dermatitis being most prominent. At present, to ensure complete coverage of the CTV, uncertainties which include patient set-up errors, target volume definition uncertainties but also internal organ motion, are taken into account by delineating a generous CTV or adding a generous margin from CTV to the planning target volume (PTV). To minimize uncertainties and consequently decrease toxicity to surrounding healthy tissue, several measures can and have to be taken.

Firstly, decrease the irradiated volume: more knowledge on recurrence patterns demonstrates that reduction of CTV in selected cases is probably safe[66]. Lowering the upper border of the CTV results in a significant reduction of the PTV volume and irradiated small bowel volume. Secondly, decrease delineation variation: the introduction of guidelines and a delineation atlas in combination with delineation workshops have shown to decrease inter-observer delineation variation[106]. Possibly, the addition of other high resolution imaging modalities such as MRI to the planning CT could reduce delineation variation even more in the future. Thirdly, with intensity-modulated RT (IMRT) more conformal treatment plans can be delivered largely reducing small bowel volumes treated with high doses[101;234]. A comparative study has demonstrated that when implementing IMRT, supine position with a full-bladder protocol (and without a belly board) maximises patient comfort and stability on set-up. Although bowel exposure was higher on the prone and supine scans without a belly board, unacceptable values predicting acute and late toxicity were on average not reached. This questions the need for the belly board next to IMRT with full bladder protocol[234]. As a consequence of the increased precision made possible with the use of IMRT it has become increasingly important to estimate and account for these uncertainties involved to prevent critical under-treatment of parts of the target volume, especially in hypofractionated treatment plans. The next step is to reduce margins but to make this possible, more knowledge on shape variation of the whole CTV during the whole treatment is required.

In *Chapter 3* we present data on inter-fraction shape variation, demonstrating that adapted CTV-PTV margins for different parts of the CTV are needed to ensure adequate coverage. In this way IMRT can be safely applied. For further margin reduction a more imaged-guided approach is warranted, with an online and adaptive approach to CTV delineation with images, acquired upon setup and before the fraction, supplying information on present patient anatomy. In patients treated with CRT a mean

reduction in rectal volume was observed over time during the treatment. A recent study has suggested that with one single plan adaption based on repeat-CT images gained during the first 4 fractions the difference between intended and treated volume (systematic error) and subsequent PTV margins can be reduced significantly[235].

In conclusion, radiotherapy is a valuable tool with additional value to surgery alone in the treatment of rectal cancer. Future refinement will include more accurate patient selection for those really in need of radiotherapy to reduce LR, while on the other hand understanding and quantification of uncertainties will lead to increased precision of dose delivery leading to a decrease in toxicity to surrounding healthy tissue but also opening up possibilities for dose escalation with boosts to maximize response.

PATHOLOGY

RESPONSE ASSESSMENT

Following the introduction of preoperative CRT for rectal cancer, histopathological features have changed, and the impact of these changes is yet unknown. Furthermore, assessment of response has become an integral part of histopathological assessment. In *Chapter 5* we demonstrate that tumours seem to respond heterogeneously to CRT, but mechanisms governing response or resistance unfortunately remain unclear.

The ypT stage can be used as a measurement for tumour shrinkage or downstaging if the pre-treatment staging was accurate. However, there is a large variability with regard to tumour load, some tumours respond with downstaging from a cT4 to a ypT2, while others show regression or fragmentation of the vital tumour with residual tumour deposits scattered throughout the mesorectal fat. Extent of regression of the tumour after CRT is assessed by semi-quantitatively scoring the relative proportion of residual tumour to stromal fibrosis, the tumour regression grade. A complete response (ypT0) is clearly associated with excellent disease control, but results of our series surprisingly show that a near pCR fares poorly *(Chapter 5)*. Various systems have been suggested to grade tumour regression, but the majority are not able to demonstrate a relation with prognosis[5;71;74;153]. In addition, reproducibility of regression grading is poor[71], especially those using many tiers, preventing the introduction of one particular system into daily practice. Our results suggest that the 4 tier regression grade may predict prognosis in a strictly defined group of LARC receiving a uniform treatment. However, further validation in a larger series is required to unravel the true prognostic meaning of different types of response.

Of note, the length of the delay between radiotherapy and surgery influences observed response rates with more response being observed after longer delays. Dependant on their position in the cell cycle, some tumour cells go into apoptosis directly after RT while others take weeks to do so. After a longer delay to surgery, relatively more radiosensitive tumour cells will have gone into apoptosis and have been replaced by fibrosis. This is visible on a slide after resection, however, morphologically, differentiation between a viable and dead tumour cell is impossible on a slide. This also indicates the possibility that tumour cells seen on the slide at response assessment could in fact already have been

dead at resection but simply had not yet been replaced. In the future it would be interesting to find ways to differentiate between viable tumour cells and (pre-apoptotic) damaged cells after RT and elucidate prognostic importance thereof.

FUTURE OF THE TNM CLASSIFICATION

The TNM staging system was originally used to describe the resected tumour more extensively, provide information on prognosis and guide the use of adjuvant therapy. If all tumours are staged according to the same system, large databases can be constructed and combined for interinstitutional or international comparisons in which different treatments or outcomes can be compared. However, TNM editions have recently been changed in rapid succession, perhaps with lacking evidential support[156;236-239]. As a consequence, this very important function of pathological staging may be lost. An illustrative example is the way lymph nodes are diagnosed: TNM 5th edition staged tumour deposits in the mesorectal fat as a node if it measured more than 3 mm, while in TNM 6th edition size was unimportant while contour guided the decision. In TNM 7th edition, no rules apply giving the pathologist room to decide. A lack of standardization creates stage migration, poor reproducibility, and major uncertainty for pathologists. In some European countries, this problem has temporarily been solved by deciding to remain with TNM 5th edition.

On the other hand, with new prognostic factors like the CRM at hand, the classification of rectal cancer needs to be refined[236;237;240]. In modern staging of rectal cancer there should be a place for treatment-related factors, given that the result of treatment strongly determines prognosis. Promising suggestions for replacing the TNM system (using only tumour related factors) with a combination of a tumour-related factor like nodal status, and a treatment-related factor like CRM, have resulted in improved prognostication with highly divergent survival curves[241]. Also, a nomogram has recently been developed as a result of a pooled analysis of 5 large European randomized trials in LARC with the aim of stratifying the risk of an event. The nomogram is able to predict local/distant control and overall survival after 5 years thereby serving as a tool to guide more intensive follow-up or adjuvant treatment in those at risk[75]. As MRI has become the standard tool for staging of LARC, the group of LARC patients treated in trials will become more uniform and well-defined, which raises possibilities for further refinement of these nomograms in the future. Last but not least, the role of molecular genetics is slowly being unravelled as an important marker for response prediction to neoadjuvant (C)RT treatment or to adjuvant treatment but also for prognosis. This will facilitate an even more patient tailored treatment using genetic information together with the abovementioned patient and treatment related factors.

With the introduction of the microarray in molecular biology, large amounts of information on gene activity can be produced in a quick and orderly fashion. An example of success booked in this field is the Mammaprint[242] which is able to distinguish a good and poor prognostic profile in lymph-node negative or minimal positive (1-3 nodes) breast cancer patients. Meanwhile, another study has reported the development of a 10-gene prediction model for intrinsic radiosensitivity, with a sensitivity

and specificity of around 80%[243]. Also, recent investigations into gene expression profiling and kinase activity profiling revealed the possibility to predict response to CRT in-vivo[244;245].

IN CONCLUSION

Rectal cancer treatment is a team effort. The different modalities with their specialists are inter-dependent when providing care of high quality. Improvements in the different modalities have improved local control immensely. Now it is time to shift attention to increasing the distant metastases-free survival and to the possibilities of less invasive surgical strategies. As technology improves, imaging for (re-)staging and delivery of radiotherapy will improve, leading to possibilities for more accurate patient selection and more precise radiotherapy delivery of more effective doses, respectively. As new neoadjuvant regimens are explored and genetic backgrounds are unravelled, treatment will become more patient tailored. The recently initiated prospective audits will shed light on the quality of delivered care with the aim of improving outcome, whilst minimizing side effects and maintaining post-treatment quality of life.

CHAPTER 9

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CHAPTER 10

Summary

(in English and Dutch)

SUMMARY

CHAPTER 1

In the first Chapter a general introduction and background is given on recent developments in the multidisciplinary approach to the treatment of rectal cancer. In the Netherlands, roughly 3500 patients are diagnosed with rectal cancer each year. Improvements across all modalities have decreased the number of tumour positive circumferential resection margins (CRM) and optimized local control. Approximately, 60% of patients are alive after 5 years, with local recurrences occurring in around 5-10% and distant recurrence up to 30% of patients.

Total mesorectal excision (TME) remains the cornerstone of treatment, while preoperative radiotherapy (RT) or chemoradiotherapy (CRT) further improves local control. Following the introduction of the MRI, patients with rectal cancer can be stratified into risk groups and treated accordingly, each with a different treatment approach based on the risk of a positive CRM and subsequent local recurrence. Patients with well differentiated, superficial tumours (T1N0) where treatment with local excision suffices, were excluded for the purposes of this thesis. The intermediate risk group consists of patients with mobile resectable tumours (T1- T3, N0-1) where the distance to the mesorectal fascia (MRF) is ≥ 1 mm. These patients receive preoperative 5x5 Gy radiotherapy (short-course radiotherapy; SCRT) followed directly by TME. Recently, TME only has become a valid option in those patients without suspected nodal disease and in those with superficial mesorectal fat invasion of the primary tumour (≤ 5 mm). The high-risk group includes patients with locally advanced tumours, where the MRF or the consequent surgical CRM is threatened or involved (distance to MRF < 1 mm), or where extensive lymph node involvement (cN2) or extra-mesorectal pelvic lymph nodes are suspected. In this group, the treatment of choice consists of preoperative downstaging with long-course radiotherapy (25x2 Gy) in combination with oral fluoropyrimidine-based chemotherapy (CRT), followed by delayed TME.

After resection the pathologist evaluates the specimen, micro- and macroscopically, and gives feedback to other caregivers on response, lymph node metastases and resection margins, and other histopathological factors governing prognosis.

CHAPTER 2

In Chapter 2 the present population-based multidisciplinary team (MDT) approach to (>T1N0) rectal cancer in the region was evaluated. According to national guidelines, all rectal cancer patients deserve preoperative MDT discussion with the aim to improve quality of staging and to optimize decision making. The value of the MDT discussion was evaluated in 210 patients diagnosed in the greater Amsterdam area. The hypothesis was that discussion in an MDT would lead to less positive CRMs.

In actual fact, in only 55% of all patients documentation was found of a discussion in an MDT. In those discussed, MRI was implemented more often and TNM staging was more complete, while more advanced patients were also discussed significantly more often. The CRM, a powerful prognosticator

in rectal cancer, was mentioned in the pathology report in only 61% of patients, and additionally measured for the purpose of this study in 34% of patients. The overall CRM rate was 13% and did not differ between those discussed and not discussed, probably because more advanced patients were selected for discussion. In theory, after accurate preoperative selection and discussion, patients undergoing SCRT or no RT should have a negative CRM after adequate TME, as otherwise preoperative CRT was probably the treatment of choice to induce downsizing and downstaging and facilitate radical resection. However, the positive CRM rate was still 10% in those judged to require preoperative SCRT (or no RT occasionally), indicating room for improvement in patient selection. In LARC patients receiving CRT, a positive CRM could unfortunately not be prevented in 20% of patients.

Results of this retrospective study demonstrate room for improvement, especially in the selection of patients for SCRT or no RT. Standardized documentation of treatment decisions and pathology reports are needed. Since then, the latter has been effectuated in daily practice. Audits but also pathologists are an important source of feedback for quality control.

CHAPTER 3

Following the establishment of the benefits of radiotherapy in the treatment of rectal cancer, radiotherapy-related side effects have to be kept to a minimum. The challenge is to minimize the dose to surrounding healthy tissue or organs at risk, whilst assuring adequate clinical target volume coverage. Internal organ motion causes shape variation of the clinical target volume (CTV) and forms a major uncertainty that governs and limits the accurate delivery of radiotherapy. To evaluate the magnitude of this uncertainty a prospective repeat CT study described in Chapter 3 was initiated. Aim was to quantify the inter-fraction shape variation of the full CTV in rectal cancer patients treated with SCRT (5x5 Gy) and CRT (25x2 Gy + daily capecitabine). Subsequently, new anisotropic planning target volume (PTV) margins, which take these uncertainties into account, were derived to replace the standard 1 cm PTV margin.

For the 33 SCRT patients CT-scans were made daily, while for the 30 CRT patients a CT-scan was made daily in the first week and weekly thereafter. The full CTV was then delineated on a total of 482 CT-scans. The calculated CTV shape variation was found to be a major and heterogeneous geometric uncertainty in both groups, with systematic and random errors ranging from 0.2 cm standard deviation (SD) close to bony anatomy to 1.0 cm SD at the upper-anterior border of the mesorectum. For the lateral lymph node regions smaller systematic shape variations were found. Male and female shape variation did not differ significantly overall.

Subsequently, gained information on shape variation was used to develop a modified recipe for a new PTV. Required anisotropic margins ranged from 0.7 cm close to bony structures up to 3.1 and 2.3 cm in the upper-anterior region for SCRT and LCRT, respectively. This results in a suggested PTV which is approximately 20% smaller than the conventional combination of a generously delineated CTV with the fixed 1cm PTV margin.

CHAPTER 4

In the treatment of LARC, 5-fluoruracil (5-FU) -based CRT has been demonstrated as an effective modality to induce downstaging and downsizing. Capecitabine is an attractive radiosensitizer with ease of oral intake compared to intra-venous 5-FU. However, few studies have concentrated on the surgical morbidity and mortality resulting from this treatment modality. In Chapter 4 acute toxicity and surgical complications associated with preoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer were evaluated. Toxicity was scored according to the Common Terminology Criteria (version 3.0) and Radiation Therapy Oncology Group scoring systems. Treatment related surgical complications were evaluated up to 30 days after discharge from hospital using pre-determined definitions and the validated modified Clavien–Dindo classification.

Some 147 patients with strictly defined LARC (M0) were included. The preoperative CRT was tolerable, with a mean cumulative chemotherapy dose of 95%, while 98% of the patients received ≥ 45 Gy. Serious toxicity (grade 3-5) was observed in 22% of the patients, especially diarrhoea and radiation dermatitis. The post-operative morbidity was significant, but did not translate into mortality in this series. Anastomotic leakage was found in 28% of the patients after LAR, while perineal wound complications occurred in 37% of the patients after an APR. One in 5 patients needed to be re-admitted within 30-days after initial hospital discharge.

These results indicate that preoperative CRT with capecitabine is associated with acceptable acute toxicity and surgical mortality but with significant morbidity. A review of the literature on morbidity revealed that our anastomotic leakage rates were higher than rates reported in randomized controlled trials and phase II studies. Complication rates were not the endpoint of these studies and definitions used were barely mentioned. Our series also contained more advanced tumours, similar to another study reporting similar rates of morbidity. An important conclusion from this study was the importance of uniform definitions to be able to inform patients on possible adverse effects and to facilitate inter-institutional comparisons so that morbidity can serve as a quality of care parameter.

CHAPTER 5

Following the introduction of preoperative CRT, the importance of histopathological parameters in rectal cancer has changed. Some rectal tumours undergo apparent complete tumour regression after CRT. Clinically undetectable residual tumour deposits or pathologic lymph nodes may remain in the mesorectum. In this Chapter efficacy of the CRT was evaluated. The objective of this study was to evaluate which factors determine outcome, focusing on the contribution of histopathological response after CRT.

Slides of 107 patients were revised according to TNM 5th edition and response scored according to 4 grades of regression. Results indicate that in this series with almost 40% cT4 tumours, CRT (25x2 Gy with capecitabine) is an effective regimen, and worth the experienced morbidity, with 20% revealing a pCR, 11% near pCR, 55% response and only 14% no response. This could partly justify the experienced

adverse effects mentioned earlier. However, alarming rates of residual lymph node metastases occurred in those with a pCR (29%) or near pCR (50%). Furthermore, islands of tumour cells were found invading the mesorectal fat in 42% of near pCR patients. Regarding the distant metastases free interval, patients with a pCR show excellent outcome, however, those with a near complete response were associated with a relatively poor outcome with 5/12 patients developing distant metastases.

With the inabilities of present day imaging to accurately identify lymph nodes metastases and distinguish fibrosis from tumour deposits, a 'wait and see' policy in LARC is associated with significant risks and should be applied with extreme care.

CHAPTER 6

As CRT results in near or complete remission in 30% of the patients, pre-treatment demarcation of the tumour location will become more important in the future. Furthermore, utilizing their radio-opaque characteristics endoclips can be implemented to aid target volume delineation during radiotherapy, aid clinical assessment of response or mark the tumour during endorectal brachytherapy. Retention rates have, however, only been evaluated in canines and pigs and have not yet been reported in the human gastrointestinal tract. In Chapter 6, long-term attachment rates of two modern, but different, endoclips used in the human gastrointestinal tract were evaluated as part of a study to evaluate the feasibility of external beam radiation therapy followed by endorectal brachytherapy. The rectal tumour was marked with Quickclips (Olympus Ltd.) and/or Resolution (Microvasive, Boston Scientific Corp) endoclips to facilitate tumour localization during the brachytherapy procedure.

A total of 44 clips were placed in 9 patients during endoscopy before or after the external radiotherapy. The attachment was evaluated during repeat endoscopy after external radiotherapy or traced on fluoroscopy images acquired every week during the brachytherapy. Results demonstrated that the Resolution clip, which has the advantage of being able to open and close its jaws repeatedly, was superior to the Quickclip (unchangeable after firing) in situations where long-term attachment is warranted. The Resolution clip remained attached longer than the Quickclip, with encouraging long-term retention rates of up to 67% for the Resolution clip after nearly 12 weeks. In contrast, only 35% of the Quickclips remained attached. A possible downside for the clinical use of endoclips arising from this study, is the fact that the endoclips are not magnetic resonance imaging (MRI) -compatible, causing artefacts on MRI. As MRI has become standard of care in staging and re-staging of rectal cancer, further research and development is required, for instance into the feasibility and retention of submucosal gold markers.

CHAPTER 7

This Chapter concerns the treatment of metastatic colorectal disease. For patients with peritoneal metastases a new treatment has been proved effective which includes extensive debulking or cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) to eradicate residual microscopic disease. Selecting patients for cytoreductive surgery and HIPEC remains

challenging. In the study reported in chapter 7, three prognostic tools are compared which are used at the beginning of the cytoreduction to select patients in which complete cytoreduction is possible, as only these patients benefit from the treatment. The peritoneal cancer index (PCI) and the simplified PCI (SPCI) both combine cancer implant size with cancer distribution. The PCI contains 13 abdominopelvic regions divided artificially by lines, while the SPCI contains 7 regions dependant on anatomical structures involved. According to tumour load a score is given to each region. The 7-region count describes the number of affected regions out of 7 in the SPCI system, regardless of the tumour volume.

Results of this study of 92 patients showed that an increased PCI, SPCI or number of regions were all associated with a decrease in probability of complete cytoreduction and subsequent overall survival. A cut-off value of 16 in the PCI system, 13 in the SPCI system and 6 regions in the 7 Region Count were most predictive of both endpoints. The three tools were equally effective prognostic tools predicting completeness of cytoreduction and associated improved survival. However, the 7 Region Count may be preferred due to its practical simplicity and has become the tool of choice in the Netherlands.

Nederlandse Samenvatting

SAMENVATTING

HOOFDSTUK 1

In het eerste Hoofdstuk van dit proefschrift wordt ter inleiding een weergave gegeven van recente ontwikkelingen op het gebied van de multidisciplinaire behandeling van het rectumcarcinoom. Verbeteringen in alle afzonderlijke modaliteiten hebben er toe geleid dat het aantal positieve resectie marges en het aantal lokale recidieven flink zijn gedaald. In Nederland worden er jaarlijks 3500 patiënten gediagnosticeerd met een rectumcarcinoom. Ongeveer 60% van deze patiënten leeft nog na 5 jaar, terwijl een lokaal recidief bij 5-10% en afstandsmetastasen bij 30% van de patiënten geconstateerd wordt. Het doel van wetenschappelijk onderzoek bij het rectumcarcinoom is enerzijds het ontwikkelen van "therapie op maat", afhankelijk van tumor- en patiënteigenschappen. Anderzijds is het belangrijk dat elke therapie gestandaardiseerd gegeven of uitgevoerd wordt om optimale kwaliteit te waarborgen. Inmiddels zijn er in Nederland richtlijnen geschreven waarin deze twee facetten verwerkt zijn.

Centraal in de behandeling van het rectumcarcinoom staat het verwijderen van de tumor middels totale mesorectale excisie (TME). Deze operatie is een *en bloc* resectie van de primaire tumor met omliggende lymfklieren in het mesorectum door middel van scherpe dissectie in het circumferentiele, avasculaire vlak van het rectum. Als aanvulling hierop, om de lokale controle verder te verbeteren, wordt voorafgaand aan de operatie bestraling (RT) of een combinatie van bestraling met chemotherapie (CRT) gegeven.

Beeldvormende technieken, MRI in het bijzonder, bieden tegenwoordig de mogelijkheid om patiënten in 3 groepen onder te verdelen afhankelijk van het risico op een incomplete resectie (een positief circumferentiele resectie marge, CRM) en lokaal recidief. Laag risico patiënten, diegene met een oppervlakkig gelegen en goed gedifferentieerde tumor (T1N0) waarbij lokale excisie volstaat, worden in dit proefschrift buiten beschouwing gelaten. De intermediaire risico groep bestaat uit patiënten met een mobiele en resectabele tumor (T1-3N0-1) met een afstand tot de mesorectale fascie (MRF) ≥ 1 mm. Deze patiënten ondergaan een korte preoperatieve bestraling gedurende 5 dagen (5x5 Gy) met als doel losse achtergebleven cellen te doden. TME volgt binnen een week. Onlangs is besloten de preoperatieve bestraling achterwege te laten bij patiënten zonder klinisch verdenking op positieve lymfklieren en bij patiënten met beperkte (≤ 5 mm) of zonder extra-murale vet invasie. Bij de hoog risico groep (cT2-3 met afstand tot de MRF < 1 mm of cT4, en/of hoge mate van waarschijnlijk op 4 of meer positieve lymfklieren binnen het mesorectum of positieve lymfklieren buiten het mesorectum op basis van MRI) is preoperatieve bestraling noodzakelijk om de tumor te verkleinen om de kans op een radicale resectie te vergroten. Dit betreft patiënten met een lokaal uitgebreid rectumcarcinoom die CRT ondergaan, een combinatie van een lang schema radiotherapie (25x2 Gy) en lage dosis chemotherapie (capecitabine). Hierna volgt een periode van rust om de tumor de kans te geven kleiner te worden, waarna chirurgie volgt 6-10 weken later met eventuele uitbreiding van de resectie naar omliggende geïnfiltreerde organen zoals de blaas, uterus of prostaat.

Na de TME wordt het preparaat door de patholoog op macroscopisch en microscopisch niveau onderzocht. Informatie over de respons op de voorbehandeling, aanwezigheid van lymfklier metastasen en de resectie marges zijn belangrijke factoren die de prognose bepalen.

HOOFDSTUK 2

In Hoofdstuk 2 wordt de multidisciplinaire aanpak van het (>T1N0) rectumcarcinoom in regio Amsterdam geëvalueerd. Volgens de geldende Nederlandse richtlijn ten tijde van het onderzoek behoren alle patiënten in een multidisciplinair team (MDT) bespreking besproken te worden met als doel stadiering en keuze van een optimaal behandelingsplan te bewerkstelligen.

In deze studie werd de aanvullende waarde van de MDT bespreking geëvalueerd in 210 patiënten met als hypothese dat bespreking in een MDT zou leiden tot minder positieve resectie marges. Het bleek echter dat slechts iets meer dan de helft (55%) van de patiënten daadwerkelijk werd besproken. Van diegene die besproken werden was de TNM stadiering vaker compleet en werd de MRI vaker geïmplementeerd. Ook werden patiënten met een verder gevorderd stadium vaker besproken. De resectie marge (CRM) werd slechts in 61% van de gevallen genoteerd en werd door ons in de overige gevallen aanvullend gemeten. Het percentage positieve CRM's was 13 % over de gehele studiepopulatie en verschilde niet tussen de besproken en niet besproken groep, waarschijnlijk omdat patiënten met een meer gevorderd tumorstadium met een hogere *a priori* kans op een positieve CRM juist geselecteerd werden voor de MDT bespreking. Theoretisch zouden patiënten na een accurate stadiering en adequate TME, na 5x5 Gy of zonder preoperatieve bestraling, geen positieve CRM moeten hebben omdat er geen sprake was van een bedreigde MRF. Het percentage positieve CRM's was 10% in deze groep. In patiënten met lokaal uitgebreide ziekte bleek de voorbehandeling en de operatie in 20% van patiënten niet voldoende om een positieve marge te voorkomen.

De resultaten van deze studie tonen aan dat er ruimte voor verbetering bestaat, vooraal in preoperatieve stadiering en selectie van patiënten voor kortdurende RT of geen RT. Gestandaardiseerde documentatie van behandelingskeuzes en PA verslagen zijn nodig. Dit laatste is sindsdien geïntroduceerd in de dagelijkse praktijk. Het uitvoeren van audits en implementeren van pro-forma's, in het algemeen, zijn nuttig voor het terugkoppelen van informatie aan de MDT en kunnen gebruikt worden om de kwaliteit te waarborgen.

HOOFDSTUK 3

Radiotherapie als (neo)adjuvante behandeling gaat gepaard met een verhoogde kans op bijwerkingen, op korte en langer termijn, zoals diarree, afwijkend ontlastingspatroon, fecale incontinentie en sexuele dysfunctie. Om de kans op bijwerking te minimaliseren moet de bestraling zo goed mogelijk aangepast worden aan alleen het te bestralen doel volume ("clinical target volume", CTV) terwijl zo min mogelijk dosis gegeven wordt aan het omliggende gezonde weefsel. Er zijn echter onzekerheden waar rekening mee gehouden moet worden zoals variatie in de definitie van het te bestralen gebied, dag tot dag vormverandering van het CTV en variatie in positionering van de patiënt op het

bestralingstoestel. Om te corrigeren voor deze onzekerheden wordt het CTV uitgebreid met een veiligheidsmarge en vormt dan het “planning target volume” (PTV). Naar mate we meer te weten komen over deze onzekerheden, door bijvoorbeeld in beeld te brengen hoe organen (en daarbij het doelvolume) bewegen tussen verschillende fracties, is de volgende stap het doelvolume en benodigde veiligheidsmarges te verkleinen. Dit was het doel van het onderzoek naar vormvariatie van de gehele CTV tijdens de preoperatieve bestraling in Hoofdstuk 3.

In deze prospectieve studie werden tijdens de voorbehandeling (5x5 of CRT), dagelijks in de eerste week en daarna wekelijks bij de CRT patiënten, CT scans gemaakt. Het CTV werd volgens strikte definities ingetekend op in totaal 482 scans. De vormverandering was heterogeen, met grote variaties aan de voorzijde bij de blaas en dunnedarm (1 cm SD) en minder grote variaties aan de laterale zijde in de lymfklier regio’s (0.5 cm SD). Bij de benige structuren was de variatie het kleinst (0.2 cm SD). Tijdens de CRT behandeling nam het rectum volume in de tijd af, hetgeen resulteerde in een afname van het CTV aan de voorzijde met gemiddeld 0.5 cm. Tussen man en vrouw verschilde de variatie niet significant.

De volgende stap na bepaling van de vormvariatie van het CTV was bepaling van de PTV marge. De algemeen bekende formules om onzekerheden te vertalen naar een CTV-PTV veiligheidsmarge zijn echter niet zonder meer te gebruiken. In hoofdstuk 3 is berekend hoe de formule moest worden aangepast voor gebruik in vormverandering en om voldoende dekking van het CTV te waarborgen. De voorgestelde marges in combinatie met een strikt ingetekend CTV resulteerde in PTV volumes die gemiddeld genomen 20% kleiner waren dan de “klassieke” klinische ruime intekeningen met een 1.0 cm marge.

HOOFDSTUK 4

Preoperatieve CRT wordt gebruikt bij het LARC om middels verkleining van de tumor een radicale resectie te faciliteren. Verschillende beschrijvende studies laten een verhoogde incidentie van naadlekkage zien na neoadjuvant (C)RT. Dit wordt echter in gerandomiseerde studies niet bevestigd. Capecitabine, een orale vorm van het intraveneuze 5-FU dat in de gerandomiseerde studies werd gebruikt, is een aantrekkelijke vervanger van 5-FU. Het toxiciteitsprofiel hiervan is nog niet uitgebreid onderzocht. In Hoofdstuk 4 werd de acute toxiciteit en chirurgische morbiditeit van preoperatieve CRT met capecitabine in 147 patiënten met LARC geëvalueerd. Toxiciteit werd met behulp van de Common Terminology Criteria (version 3.0) en de Radiation Therapy Oncology Group scoring systemen geëvalueerd. Chirurgische complicaties werden gescoord tot 30 dagen na ontslag uit het ziekenhuis met behulp van vooraf bepaalde definities en de gevalideerde gemodificeerde Clavien-Dindo classificatie.

De preoperatieve CRT werd goed getolereerd met een gemiddelde cumulatieve chemotherapie dosis van 95% van de geplande dosis, terwijl 98% van de patiënten tenminste 45 Gy van de 50 Gy heeft ontvangen. Ernstige toxiciteit (graad 3-5) werd door 22% van patiënten ondervonden, vooral diarree en bestralingsgerelateerde huidafwijkingen. Eén patiënt is ten gevolge van een pancytopene

sepsis overleden tijdens de CRT. De postoperatieve morbiditeit was aanzienlijk, maar dit liet zich niet vertalen in mortaliteit (0%). Naadlekkage werd bij 28% van de patiënten na een LAR geconstateerd, terwijl perineum wond complicaties werden gezien in 37% van diegenen die een APR ondergingen. Eén op 5 patiënten moest worden heropgenomen in het ziekenhuis binnen 30 dagen na ontslag.

In deze relatief grote serie patiënten die preoperatieve CRT met capecitabine had ondergaan, was de acute toxiciteit acceptabel, de chirurgische morbiditeit aanzienlijk maar de mortaliteit laag. Een mogelijke verklaring voor de hoge morbiditeit zijn de ruime definities die gehanteerd werden in deze studie. Door een grote variatie in de gehanteerde definities van naadlekkage en perineumwond complicaties is vergelijking tussen studies moeilijk. Een uniforme definitie zal inter-institutionele vergelijkingen beter mogelijk maken.

HOOFDSTUK 5

Preoperatieve CRT gevolgd door TME 6-8 weken later geeft goede lokale controle, waardoor de ontwikkeling van afstandsmetastasen de prognose nu lijkt te gaan bepalen. Door de CRT veranderen echter de histolopathologische kenmerken na de behandeling, waarvan de prognostische betekenis nog onduidelijk is. Sommige tumoren gaan als gevolg van de CRT in volledige regressie met als resultaat volledige fibrosering van het gebied of vorming van slijmmeren. De literatuur beschrijft dat een complete respons geassocieerd is met een uitstekende prognose. Chemoradiotherapie zonder chirurgische resectie (of alleen lokale excisie) in geval van complete klinische remissie (het zogenoemde “wait and see” beleid) heeft geleid tot veelbelovende resultaten. Potentiële (negatieve) gevolgen hiervan, zoals achtergebleven microscopisch resten of klier metastasen die vooralsnog niet detecteerbaar zijn met de huidige beeldvormende technieken, moeten nog verder onderzocht worden. Doel van het retrospectieve onderzoek besproken in dit hoofdstuk was om de uitkomst na CRT te evalueren en de histopathologische voorspellers van tumor respons en uitkomst op langer termijn te evalueren.

De coupes van 107 patiënten werden gereviseerd volgens TNM 5de editie. Mate van respons van de primaire tumor werd gescoord (volgens ‘tumor regression grade’ of TRG) en ingedeeld in 4 groepen. In deze serie van bijna 40% cT4 tumoren bleek CRT zeer effectief te zijn; 20% van de patiënten had een pathologische complete respons (pCR), 11% een bijna complete respons (near-pCR), 55% liet een (partiële) respons zien en 14% liet geen respons zien. Lymfklier metastasen werden gevonden bij 29% van patiënten met een pCR en bij 50% met een near-pCR. Daarnaast werden bij de near-pCR groep kleine tumor restjes reikend tot in het mesorectale vet bij 42% van de patiënten gevonden. Patiënten met een pCR in onze serie hadden een zeer goede uitkomst. Diegene met een near-pCR hadden een onverwacht slechte uitkomst, 5 van de 12 patiënten ontwikkelden afstandsmetastasen.

Met de huidige beeldvormende technieken is het momenteel niet goed mogelijk lymfklier metastasen of microscopische resten in voldoende mate te kunnen identificeren of te onderscheiden van fibrose als gevolg van CRT. De mogelijkheid van een ‘wait and see’ beleid bij patiënten met een LARC die CRT

ondergaan is momenteel dan ook geassocieerd met de nodige risico's en moet met terughoudendheid en voorzichtigheid toegepast worden.

HOOFDSTUK 6

Aangezien 30% van patiënten na preoperatieve CRT een pCR of een near-pCR bereikt zal het markeren van de tumor in het rectum tijdens de behandeling van toenemend belang gaan worden. Endoclips die met röntgenstraling detecteerbaar zijn kunnen onder andere gebruikt worden om een tumor te markeren om klinische respons te meten of om een doelvolume te markeren tijdens brachytherapie (inwendige radiotherapie). Onderzoek naar hoe lang deze endoclips vast blijven zitten (retentie) blijft beperkt tot dierproeven en is niet eerder in het menselijke darmstelsel onderzocht. In Hoofdstuk 6 werd de mate van retentie op lange termijn van twee moderne endoclips prospectief geëvalueerd als deel van een studie naar definitieve radiotherapie (gecombineerd uitwendig en inwendige bestraling) als behandeling bij medisch inoperabele patiënten. Het rectum tumor werd met Quickclips (Olympus Ltd.) en/of Resolution (Microvasive, Boston Scientific Corp) endoclips gemarkeerd om de tumor te lokaliseren tijdens de brachytherapie.

In totaal werden er met de endoscoop 44 endoclips geplaatst in 9 patiënten voor of na de externe radiotherapie. Retentie van de endoclip werd bepaald bij vervolg endoscopie na de externe radiotherapie (echter voor de start van de brachytherapie) of met behulp van röntgenfoto's tijdens de wekelijkse brachytherapie. De Resolution endoclip, die over de mogelijkheid beschikt herhaaldelijk zijn tanden te openen en sluiten, bleek gemiddeld langer te blijven zitten (retentie van 67% na bijna 12 weken) dan de Quickclip (35% retentie), die na eenmaal afgeschoten te zijn niet meer van positie kan veranderen. Een nadeel van deze endoclips is het feit dat ze niet bruikbaar zijn in de MRI, aangezien ze voor artefacten zorgen. Derhalve dient verder onderzoek plaats te vinden naar andere markeringstechnieken, bijvoorbeeld met behulp van submucosale goud markers.

HOOFDSTUK 7

Hoofdstuk 7 betreft de behandeling van patiënten met gemetastaseerde ziekte, in het bijzonder patiënten met peritoneale metastasen. Diverse onderzoeken hebben aangetoond dat cytoreductieve chirurgie gevolgd door Hypertherme Intraperitoneale Chemotherapie (HIPEC) een betere overleving geeft dan chemotherapie alleen bij patiënten met peritoneale metastasen van colorectale oorsprong. Echter, alleen patiënten bij wie een complete cytoreductie (residu na chirurgie <2.5 mm) is bereikt, blijken voordeel te ondervinden van deze ingrijpende behandeling. Momenteel worden er verschillende scoring systemen gebruikt om aan het begin van de operatie een schatting te maken of complete cytoreductie haalbaar is: 1) de Peritoneal Cancer Index (PCI), deelt het abdomen in 13 regio's met lijnen en bepaald de hoeveelheid tumor per regio; 2) de Simplified Peritoneal Cancer Index (SPCI) gebruikt 7 regio's die gerelateerd zijn aan anatomische structuren en bepaald ook de hoeveelheid tumor per regio; 3) en de 7 Region Count, die uit dezelfde 7 regio's bestaat als de SPCI maar die alleen scoort als regio is aangedaan. Het doel van de studie beschreven in Hoofdstuk 7 was het vergelijken

van de doeltreffendheid van de in Nederland gehanteerde SPCI met de 7 Region Count en de PCI. Vervolgens werd het voorspellende karakter van de 3 scorings systemen op complete cytoreductie en mediane overleving bepaald.

Uit deze studie met 92 patiënten bleek dat bij alle scorings systemen een oplopend aantal punten of aangedane regio's geassocieerd was met een verminderde kans op complete cytoreductie. Met een afkapwaarde van 16 punten uit 39 bij de PCI, 13 uit de 21 bij de SPCI en 6 aangedane regio's bij de '7 Region Count' waren de systemen het meest voorspellend en nam de overleving het sterkst af. De drie scorings systemen waren allen even effectief in het voorspellen van een complete cytoreductie en de resulterende overleving. De 7 'Region Count' die, wegens zijn praktische eenvoud, de voorkeur verdient wordt sindsdien in Nederland gebruikt.

Appendices:

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CURRICULUM VITAE

Hendrik Albert Maurits Swellengrebel werd op 7 oktober 1979 geboren in Somerset-West, Zuid-Afrika. Na het behalen van zijn eindexamen aan de Parel Vallei High School, is hij naar Nederland gegaan om aldaar te gaan studeren en de Nederlandse taal te leren. Nadat hij in de zomer van 1998 de staatsexamens 4-6 VWO in 10 weken heeft bestudeerd en behaald, is hij ingeloot voor de studie geneeskunde aan de Universiteit van Utrecht. Tijdens zijn studie heeft hij verschillende coschappen gelopen in Kaapstad (Tygerberg ziekenhuis) en een pilot onderzoek opgezet op de afdeling longziekten van het Monash University Medical Centre, Melbourne, Australië onder leiding van Prof. dr. P. Bardin. Gedurende het laatste jaar van zijn studie verrichte hij onderzoek onder leiding van dr. V.J. Verwaal in het Nederlands Kanker Instituut – Antoni van Leeuwenhoek in Amsterdam. Zijn oudste coschap en eerste baan als (zaal)arts, na het behalen van zijn artsenbul in mei 2005, volgden in hetzelfde Instituut onder leiding van dr. F. van Coevorden. Aansluitend begon hij in 2008 aan een promotietraject onder leiding van Prof. dr. C.A.M. Marijnen en dr. A. Cats, waarin verschillende aspecten van de multidisciplinaire behandeling van het rectumcarcinoom, lokaal gevorderde tumoren in het bijzonder, werden onderzocht, hetgeen tot dit proefschrift heeft geleid. Daarnaast is hij als studiecoördinator betrokken geweest bij het opzetten en uitbreiden van de CRITICS studie, een internationale, gerandomiseerde fase 3 studie naar de behandeling van het maagcarcinoom, onder leiding van dr. A. Cats, Prof. dr. C.J.H. van de Velde en Prof. dr. M. Verheij. Inmiddels zijn meer dan 500 van de 788 benodigde patiënten geïncludeerd in ongeveer 50 ziekenhuizen, over 3 landen verspreid. In januari 2011 is hij gestart met de opleiding heelkunde in het Medisch Centrum Alkmaar in de regio VUMC (Opleiders dr. W.H. Schreurs en dr. D.L. van der Peet). In zijn tweede jaar heeft hij besloten een ander weg in te slaan binnen de geneeskunde.

Hendrik Albert Maurits Swellengrebel was born on the 7th of October 1979, and raised in Somerset-West, South Africa. After graduating from the Parel Vallei High School he departed for the Netherlands to start his tertiary education and to learn the Dutch language. After passing the entrance exams he started medical school at the University of Utrecht. During his studies he followed trauma, neurology and ENT internships at the Tygerberg Hospital in Cape Town, and performed a pilot study under guidance of Prof. dr. P. Bardin at the Respiratory Department of the Monash University Medical Centre, Melbourne, Australia. In his last year of training he performed research into the treatment of peritoneal metastases under guidance of dr. V.J. Verwaal at the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital in Amsterdam. His last internship, but also his first job as a medical doctor after graduating in May 2005, followed in the same hospital under the guidance of dr. F. van Coevorden. Thereafter, he started his PhD in 2008 under guidance of Prof. dr. C.A.M. Marijnen and dr. A. Cats investigating different aspects of the multidisciplinary treatment of rectal cancer, locally advanced tumours in particular, which has resulted in this thesis. He combined his research work with his function as study coordinator of the CRITICS study, an international multicentre randomized trial investigating the treatment of gastric cancer under guidance of dr. A Cats, Prof. dr. C.J.H. van de Velde and Prof. dr. M. Verheij. Presently, more than 500 of the 788 required patients have been enrolled in

over 50 hospitals in three different countries. In January 2011 he started his surgical residency at the Medical Centre in Alkmaar under guidance of dr. W.H. Schreurs, and in his second year he decided to take a different path in his practice of medicine.

LIST OF PUBLICATIONS:

1. Multidisciplinary discussion and management of rectal cancer: A population-based study.
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   Jasper Nijkamp, Maurits Swellengrebel, Birgit Hollmann, Rianne de Jong, Corrie Marijnen, Corine van Vliet-Vroegindeweij, Baukelien van Triest, Marcel van Herk, Jan-Jakob Sonke.
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   Submitted

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6. Quantitative intra-operative assessment of peritoneal carcinomatosis – A comparison of three prognostic tools.
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