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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. In 2010, 12755 patients were diagnosed with colorectal cancer in the Netherlands. Of these, 3667 (29%) were located in the rectum. 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 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 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 and the US 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. Regarding the accuracy of the different staging tools at hand, Bipat 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. 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. 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, 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-fluorodeoxyglucose tracer is increasingly being applied to evaluate metastatic or recurrent disease but presently has no role in initial preoperative staging. 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.
Chapter 1

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. Heald was the first European surgeon to publish superior local control resulting from a new surgical technique: total mesorectal excision (TME). 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 reported a LR rate of 6% after 5 years and this was confirmed by other single-centre series like Enker et al 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 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%, 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.

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.
Introduction

Figure 3 depicts a macroscopic complete rectal resection specimen after TME surgery. Reprinted with permission © 2013 American Society of Clinical Oncology. All rights reserved.

The Swedish Rectal Cancer Trial 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. 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. An important finding was that SCRT followed directly by TME does not compensate for tumour positive resection margins. 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. 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. 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\textsuperscript{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%\textsuperscript{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%\textsuperscript{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\textsuperscript{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\textsuperscript{6,37,38} which has led to investigations into a non-operative ‘wait and see’ policy\textsuperscript{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 \textit{et al}\textsuperscript{39} have published encouraging results after omitting TME, which have been confirmed by another smaller series\textsuperscript{40}. However, concerns have been expressed by others\textsuperscript{41} demonstrating that only 30% of patients with a clinical complete response actually have a pCR. Advanced imaging techniques, such as diffusion weighted MRI\textsuperscript{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% of T2 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.

DEMACRATION 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 and is not possible in a fifth of patients. Perineal wound complications after abdominoperineal resection (APR) occur in up to 34% 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, but this has not been reproduced in the randomized controlled trials. 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 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. 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, while sexual dysfunction occurs in more than half of patients 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. The German Rectal Cancer Study Group trial 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. 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. Sexual dysfunction occurred more frequently in the radiotherapy arm. 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. 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 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\textsuperscript{63}. These uncertainties are taken into account by expanding the CTV with a safety margin to a PTV\textsuperscript{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\textsuperscript{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\textsuperscript{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.

\textbf{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\textsuperscript{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 state that the 5th TNM version (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 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 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 implementing TME in the same period and led to fewer positive margins and less residual disease. In a review, Nagtegaal et al 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.

After the introduction of neoadjuvant (C)RT histological alterations occur of which the prognostic value is yet to be defined. 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 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.
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. 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. Furthermore, no significant gain in survival was observed when adding CT to RT followed by surgery in rectal cancer patients. 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\textsuperscript{79}, while in another study in the same period benefit was found in colonic cancer but not for rectal cancer\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 \textit{et al}\textsuperscript{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\textsuperscript{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%\(^8\). 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\(^9\). 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.
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.