INTRODUCTION
**Epidemiology or rectal cancer**

With approximately 610,000 deaths in 2008, colorectal cancer is the 4th in cancer specific mortality worldwide, after lung, stomach and liver cancer (WHO). International trends indicate that the incidence rates of colorectal cancer are rising, especially in economically transitioning countries [1]. The increase in these countries may reflect the adoption of western lifestyles and behaviours. Many of the established and suspected modifiable risk factors for colorectal cancer, including obesity, physical inactivity, smoking, heavy alcohol consumption, a diet high in red or processed meats, and inadequate consumption of fruits and vegetables, are also factors associated with economic development or westernization [1].

In the Netherlands colorectal cancer has the 2nd largest incidence of all cancer types after breast cancer, with a total of 12,319 new cases in 2009 (iKCnet.nl). During the 90’s approximately 25% of the colorectal cancers were in fact carcinomas in the rectum, being defined as carcinomas in the last 15 cm of the large bowel. In the recent years the percentage steadily increased up to approximately 29% in 2008. The raising incidence of rectal cancer resulted in an increase from approximately 2000 patients per year in the 90’s to 3500 patient per year nowadays (Fig. 1.1). So far, there are no reasons to believe that this trend will change in the coming years. Rectal cancer is more predominant in males (60%). Despite the increase in incidence, the mortality rates per year have remained steady, with around 850 patients per year (Fig. 1.1). The 5-year survival rates improved from about 50% in the early 90’s to around 65% nowadays and survival is mainly dependent on the advancement of the cancer at diagnosis and the possibility to remove all tumor cells at surgery.
Most patients with rectal cancer are unaware of their disease until they are confronted with a changed defecation pattern or anal blood loss. Approximately half of the rectal cancers are already advanced on the time of diagnosis. Starting in 2013, screening programs will be introduced in the Netherlands in order to detect colorectal cancers in an earlier stage and improve the survival while reducing morbidity.

**Disease staging**

There are several scoring systems for staging of rectal cancer, such as the Dukes classification and the more widely used UICC Tumor-Node-Metastasis (TNM) classification [2]. The tumor classification is in 4 stages being T1) tumor invades the submucosa; T2) tumor invades the muscularis propria; T3) tumor invades through the muscularis propria into the submucosa or into the perirectal tissue; T4) tumor directly invades/penetrates surrounding organs/structures. Nodal disease is divided into 3 stages being N0) no regional nodal involvement; N1) metastatic disease in 1 to 3 regional lymph nodes; N2) metastatic disease in 4 or more regional lymph nodes. Metastatic disease is classified in M0 and M1, being distant metastasis not present or present, respectively. Any combination of TNM is possible, and combinations can be further classified into disease stage I – IV, being I) T1-2 N0 M0; II) T3-4 N0 M0; III) T1-4 N1-2 M0 and IV) T1-4 N0-2 M1. The TNM stage is defined as cTNM when based on clinical findings, as yTNM after (chemo-) radiation and pTNM when based on pathology.

**Treatment of rectal cancer**

The treatment of rectal cancer patients has evolved significantly over the past 30 years, which has resulted in improved local control and overall survival. Extensive surgical therapy for rectal cancer has been the standard of care for many decades, after William Ernest Miles first described the abdominoperineal (APR) resection in 1908 [3]. Abdominoperineal resections involve removal of the anus, the rectum and part of the sigmoid colon along with the associated (regional) lymph nodes, through incisions made in the abdomen and perineum. Sphincter saving surgery, described as low-anterior resection (LAR), was developed later in the 20th century for rectal tumors located several centimeters from the anal verge to reduce morbidity. A major step in improvement of local control and survival was the standardization of surgery to the so-called Total Mesorectal Excision (TME), first described by Heald et al. [4] in 1979. The principle of a TME is to excise the rectum, with its surrounding soft tissue and lymphatics, as an intact unit covered by the mesorectal envelope. A successful TME specimen with an intact mesorectum will for the majority of patients result in negative tumor margins, not leaving tumor cells in the pelvic area. In a review of the first 465 patients operated by Heald et al. the superiority of a TME compared to historic surgical techniques was shown, with local recurrence (LR) rates of 6% at 5 years and 8% at 10 years [5], compared to historical numbers between 15 and 50% [6]. These single center low LR rates were later confirmed in several multi-center trials [7].

Nowadays there is a tendency to treat early stage T1N0 rectal cancers with a local excision such as transanal endoscopic microsurgery (TEM), instead of a TME. These procedures result in lower morbidity and mortality at a small cost of local control [8].
Introduction

The most important prognostic factor for prediction of LR, distant metastases (DM) and overall survival (OS) is the circumferential resection margin (CRM) [9], which is defined positive when tumor cells are found within 1 mm from the surgical resection margin. The CRM can be predicted on pre-treatment magnetic resonance (MR) images by assessing the distance between the tumor/positive lymph node borders to the mesorectal fascia (MRF). Treatment options are dependent on the pre-treatment assessment of MRF involvement.

Neo-adjuvant chemo- and radiotherapy in rectal cancer

Although local recurrence rates have dropped from approximately 30-50% to 10% or less with the introduction of the TME procedure there is still room for improvement by adding (neo-) adjuvant (chemo-) radiotherapy. The aim of (neo-) adjuvant therapy is to decrease the risk of local and distant recurrence within the limits of acceptable morbidity.

For (neo-)adjuvant radiotherapy in resectable rectal cancer two general treatment schedules are used, being short-course RT with 25 Gy in 5 fractions delivered in one week (SCRT) and long-course RT of 45-50 Gy in 25-28 fractions of 1.8-2.0 Gy (LCRT). In the past decades it has been debated when to add radiotherapy and/or chemotherapy, what fractionation scheme should be used and whether it had to be given before or after surgery. In the next section the key-trials which were conducted to answer these questions are described.

The question whether long course chemo-radiotherapy (CRT) in stage II and III resectable disease should be given in a adjuvant or neo-adjuvant setting has been answered by the German pre- vs. post-operative CRT trial [10]. The neo-adjuvant CRT arm of the trial showed better compliance, lower LR rates and lower acute- and long-term side effects. In the subgroup of patients that were pre-treatment judged by the surgeons to undergo an APR, the rate of sphincter preserving surgery was doubled after pre-operative CRT compared to the post-operative CRT patients. In this trial no difference in DM, disease-free and overall survival was observed. CRT is therefore generally done in a pre-operative setting.

The use of LCRT as sole neo-adjuvant treatment in rectal cancer patients has been abandoned based on the EORTC 29921 [11] and the FFCD 9203 [12] trials. In the EORTC 29921 trial the use of LCRT was compared to LCRT plus fluorouracil (FU) based chemotherapy (CRT). Simultaneously, the addition of adjuvant chemotherapy was tested, resulting in a 2x2 design randomized trial in advanced T3-4 resectable rectal cancer. The interval between the neo-adjuvant treatment and surgery was between 3 and 10 weeks. The CRT resulted in lower LR rates, smaller tumors, less advanced pathological tumor and nodal stages and less frequent lymphatic, venous and perineural invasion compared to LCRT. However, no improvement in progression-free and overall survival was shown [11]. The reduction in tumor size did not result in more sphincter saving surgery. The adjuvant chemotherapy did not result in improved progression-free and overall survival [11]. In an exploratory subgroup analysis on the patients with a negative CRM and M0 disease at surgery the addition of adjuvant chemotherapy seemed to be effective in patients with down staged ypT0-2 tumors [13].
In stage I - III resectable rectal cancer the addition of preoperative SCRT to TME surgery compared to TME alone results in significant reduction of the LR rate [14, 15] in patients with a negative CRM after surgery. In this setting a positive CRM is the most important predictor for LR, indicating that SCRT can not fully compensate for the inability to remove all tumor cells at surgery. Because of the short time between RT and the TME no down staging of the rectal cancer or reduction in the number of patients with a positive CRM is observed [16]. The beneficial clinical effect of SCRT in CRM negative patients is correlated to the TNM stage. In TNM stage I disease, the low incidence of LR is relatively reduced significantly, but the absolute reduction if clinically less relevant. For higher stage disease the higher incidence of LR and lower OS are improved to a clinical relevant level with SCRT [14].

The use of SCRT versus CRT has been compared in a Polish (n=312) [17] and an Australian (n=326) [18] randomized study. In both studies the acute grade III and IV toxicity was lower in the SCRT group, while late toxicity, LR and OS did not differ significantly. Because of the small sample size in both studies no definitive conclusions can be drawn on LR and OS differences between both treatment schedules and the discussion on what treatment is best still continues.

The ultimate trial in radiotherapy as sole neo-adjuvant treatment is the ongoing Stockholm III trial, in which patients are randomized between SCRT with immediate surgery (within 1 week), SCRT with delayed surgery (4-8 weeks) and LCRT with delayed surgery. The potential effects of a longer waiting period after SCRT are downsizing of the tumor and subsequent reduction in CRM positivity and increase in sphincter preserving surgery, however none of these effects are amongst the primary or secondary endpoints in the trial. Based on the first 303 patients no significant differences in compliance and severe acute toxicity between the 3 arms were shown [19]. Unfortunately, with 303 patients between 1998 and 2005, accrual for the Stockholm III trial is low.

Delayed surgery after SCRT is more often used for advanced rectal cancer patients who are ineligible for CRT. Despite high age and advanced disease in these patients, the schedule is generally well tolerated and radical surgery is possible in a considerable part of the patient population [20, 21].

In a recent meta-analysis on the biologic effective dose and fractionation by Viani and colleagues [22] both short-course and long-course neo-adjuvant RT with a biological equivalent dose above 30 Gy was shown to significantly reduce overall mortality compared to surgery alone (odds ratio SCRT 0.87 and LCRT 0.77, p=0.03 and p=0.04, respectively). Also in the Dutch TME trial, for the subgroup of TNM stage III patients with a negative CRM the 10-year survival was significantly higher for RT + TME compared to TME alone (50 vs. 40%, p=0.032) [14]. So in the broader picture, and for certain subgroups, neo-adjuvant RT not only improves local control, but also overall survival.

In summary, the above described results for SCRT, LCRT and CRT show that neo-adjuvant treatment in early and advanced stage resectable rectal cancer patients operated with TME surgery results in a reduction of local recurrences, with no or a minor improvement in progression free and overall survival. With a maximum LR reduction of approximately 9% in the EORTC trial [11] relatively many patients need to be treated with neo-adjuvant treatment to prevent one LR. The MRC-CR07 trial, comparing pre-
operative SCRT with selective post-operative CRT when the CRM was positive, was designed to evaluate whether it is possible better select patients which benefit from additional treatment. It was, however, shown that the SCRT resulted in significantly lower LR rates than selecting patients for CRT that have a positive CRM [15].

Based on the evidence from literature one might argue that for T1-2N0 rectal cancer TME surgery alone should be the treatment of choice. For T3N0 cancer without MRF involvement there is the option to add SCRT for local control, while for resectable T4N0 disease CRT should definitely be added. For patients with nodal involvement neo-adjuvant treatment is needed, but debates are ongoing whether this should be SCRT, SCRT with delayed surgery or CRT, depending on country, distance to the MRF and T-stage. For stage III rectal cancer with expected involvement of the MRF neo-adjuvant chemo-radiotherapy should be given to improve local control, and in patients with significant down staging adjuvant chemotherapy might be added. Discussion on how to treat a patient are further complicated by possible discrepancies in the studies between clinical staging, based on imaging, and pathological staging.

An alternative treatment schedule gaining popularity is the “wait and see” policy, introduced by Habr-Gama et al. [23]. After neo-adjuvant treatment of rectal cancer between 10 to 40% of patients have a complete pathological response, where no tumor cells are found in the surgical specimen. In the “wait and see” policy, patients with a clinical complete response are not operated, but an intensive follow-up scheme is used for monitoring. Assessing a clinical complete response is, however, only reliably possible when using advanced imaging such as diffusion weighted MRI [24]. This weakness was especially pointed out by Glynne-Jones et al. [25] who showed in a review that approximately only 30% of the clinical complete responders are also pathological defined complete responders. Until this technique has reached clinical routine, there is reluctance to implement the “wait and see” policy widely. As an intermediate approach, instead of using the “wait and see”, good responders can also be operated using the minimal invasive TEM procedure. If the resection margins turn out to contain residual tumor or down staging is insufficient, a TME can be performed after all, as is the design in the ongoing Dutch CARTS study.

For patients with non-resectable rectal cancer, neo-adjuvant CRT is generally used to achieve down staging and downsizing to facilitate a curative resection. A major challenge in the treatment of these tumors is assessing the response and operability after CRT on MR scans, since it is hard to distinguish tumor from fibrosis [26]. In general, patients with non-resectable rectal cancer will have very poor prognosis, except for patients with a very good response to neo-adjuvant CRT. The remainder of this thesis will focus on pre-operative SCRT and CRT in resectable rectal cancer only.

**Radiotherapy target volume and treatment delivery**

Radiotherapy is a local therapy, and therefore a target volume needs to be defined. In RT, three different target volumes are generally defined, being the gross tumor volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV). The GTV in rectal cancer is defined as the visible tumor and involved lymph nodes. The CTV is the GTV plus the volume that is suspected to contain microscopic tumor extensions. Since
microscopic extensions are not visible on medical images, anatomical guidelines for CTV definition have been developed [27]. These guidelines include all regions of the pelvic area at risk for a local recurrence when not irradiated. The CTV is typically defined by manual delineation on a planning computed tomography (CT) scan. In order to ensure that the CTV is receiving the intended dose one should take the uncertainties in preparation and delivery of RT into account. These uncertainties consist of CTV delineation variation, setup variation of the patient with respect to the treatment machine and shape/position variation of the CTV within the patient [28]. Geometric uncertainties are divided into 2 major components, being the systematic and the random errors. The systematic errors describe the average differences between what was intended to be treated and what was treated, while random errors describe the day-to-day variation. The uncertainties are taken into account by expanding the CTV with a safety margin to a PTV [29]. The larger the PTV margin, the more certain it is that the CTV will receive the prescribed dose, but simultaneously, also more healthy tissue will be irradiated, with risk of morbidity. Systematic errors have a larger effect on the dose delivered to the CTV than random errors and are therefore the major contributors to the size of the PTV margin.

The planning and delivery technique of radiotherapy has improved greatly over the past 30 years. In the early years RT delivery was performed using 2 opposing large rectangular fields. With this technique a cube of dose was delivered involving almost the whole pelvis and not shaping the dose to the PTV. An improvement in conforming the dose to the PTV was made with the introduction of 3- and 4- field box techniques. Each beam was rectangle shaped and the size was defined by the outer borders of the PTV. With the introduction of the multi-leaf collimator the shape of each beam could 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 (IMRT), where typically 7 beams from different angles are subdivided into segments, for which the intensity can be varied. With IMRT the conformality and homogeneity of the dose to the PTV is further improved [30, 31]. Besides having a limited number of beam angles (step and shoot) the IMRT can also be delivered in a continuous rotational fashion during which the collimator, rotation speed and intensity are modulated (intensity modulated arc therapy (IMAT)).

Each of the above described improvements in RT delivery resulted in more conformality to the PTV, and subsequently lower dose to the surrounding healthy tissues. As described, nowadays a CTV is delineated on a CT scan and expanded to a PTV for which a treatment plan is calculated. In the days that CT and 3D treatment planning systems were not available, treatments were designed by defining field borders based on bony anatomy on fluoroscopic images. These advancements with CT based planning have led to reduced irradiated volumes [32]. In the Swedish rectal cancer trial, running from 1987 to 1990, the cranial border of the treatment fields was set at the mid-L4 level [33]. In the later designed Dutch TME trial, running from 1996 to 1999, the cranial border of the treatment fields was lowered to the promontory at the L5/S1 level [34]. Nowadays the cranial border of the CTV is defined by the bifurcation of the iliac artery into the internal and external iliac, and typically a 1 cm PTV margin is added to create the PTV [27].
**Image-guided radiotherapy**

The geometric errors in radiotherapy can be measured in images of the patient acquired at the treatment machine. In image-guided RT (IGRT) corrections are based on these measurements, with the aim to reduce the geometrical uncertainties [35]. When available, IGRT corrections can be applied directly before start of the treatment fraction, called online correction, aiming to correct both the systematic and random errors. When processing is needed to measure the error, or daily imaging is not feasible, corrections can also be applied in an offline fashion in the subsequent fraction. However, statistical models are generally needed to assure that the applied correction is correcting the systematic error, and is not influenced by the day-to-day changing random error [36, 37].

**Fig 1.2:** Example of a modern image-guided radiotherapy linear accelerator equipped with both a portal imaging device (white arrow) and a kV cone-beam CT system (black arrows) with the flat panel on the left and the x-ray source on the right.

The available imaging devices have also evolved over the past 30 years [35]. At first, portal films were used to image the exit dose of the treatment fields. On these films it was possible to visualize the bony anatomy position with respect to the field edges. These portal films were later replaced by electronic portal imaging devices (EPID), providing similar information, but then digitally. With knowledge of the bony anatomy position with respect to the treatment fields it is possible to correct for the setup of the patient by, for example shifting the treatment table [36, 37].
To further reduce geometric uncertainties, soft-tissue contrast is needed to measure the positional variation of the CTV. For most treatment sites, such as rectal cancer, introduction of new equipment, such as the in-room CT on rails, kV- and MV-cone-beam CT (CBCT) and Tomotherapy was needed in order to visualize soft tissue [35]. When the position of the CTV is localized just prior to treatment, the easiest direct correction that can be made is a simple couch shift. When shape changes of the CTV occur, treatment fields have to be adapted to conform to the new shape [38]. These adaptations demand for a re-calculation of the planned dose for quality assurance, and are therefore not commonly applied. Pragmatic applications are sometimes used when there is an apparent systematic anatomic change by acquiring a new planning CT scan and calculating a new treatment plan.

To assess a setup error, or a positional shift of the CTV with respect to the bony anatomy, automatic registration of the in-room image with the planning CT is important. With bony anatomy being clearly visible on CT images, automatic registration can be performed reliably and fast. Registration of the CTV is generally much more challenging due to less contrast with respect to surrounding tissue. To help registration, fiducial markers can be implanted within or near the CTV to gather the marker displacement as a surrogate for the CTV displacement. This is, for example, generally done in prostate cancer RT.

Assessing shape variation of the CTV demands deformable image registration, which is highly challenging. The challenge lies in the assurance that tissues which are registered on top of each other are actually the same. Deformable image registration has not reached the clinics yet, but a lot of effort is invested [39].

In RT of rectal cancer only corrections of the setup error are generally used [40]. In SCRT, with relatively high dose per fraction, the setup errors are corrected online. In LCRT, where daily imaging is not common and fraction dose is about 2 Gy, setup errors are corrected offline.

Radiotherapy induced toxicity
While addition of (chemo-) radiotherapy to surgery improves local control, it also comes with an increase in acute and late toxicity. As toxicity is correlated to the exposure of organs at risk, the changes in RT delivery and planning have changed the occurrence of toxicity. Conventional RT delivery using 2 opposing fields has been associated with an increase in post-operative mortality in the Stockholm I trial, especially in elderly, compared to surgery only [34]. This was also seen in the Swedish rectal cancer trial where a subset of patients was treated using 2 opposing fields [33]. With 3- or 4-field techniques post-operative mortality was not different anymore between SCRT + TME and TME alone (around 3-4 %) [33, 34]. Undergoing an APR after SCRT is also associated with increased perineal wound healing problems (48% vs. 41% [42]). As a late effect, SCRT is associated with increased faecal incontinence (62% vs. 38% [42]), a doubled bowel frequency [44], anal blood loss (11% vs. 3% [43]) and impaired sexual functioning [45].

In the Polish trial, comparing SCRT to CRT, treatment related early toxicity grade 3 and 4 was significantly lower in the SCRT group (3% vs. 18% [17]). In the German trial, comparing pre- to post-operative CRT, grade 3-4 late toxicity, such as chronic diarrhea
and small bowel obstruction, was lower in the pre-operative arm (14% vs. 24% [10]).

The major organ at risk in RT of rectal cancer is the small bowel. The volume of small bowel receiving 15 Gy can be used to predict grade 3 acute diarrhea [46], while the volume receiving 45 and 50 Gy is predictive for late toxicity such as bowel obstruction and strictures requiring surgery [47, 48]. Several measures are available for small bowel dose reduction, such as irradiating with a full bladder, using more conformal delivery techniques such as IMRT, or positioning the patient on a belly board to push the small bowel away from the high dose region.

**Challenges and improvements in RT of rectal cancer**

As described, neo-adjuvant short- and long-course RT are used to increase local control, but a relatively large number of patients need to be treated to prevent one local recurrence and RT is associated with increased acute- and late-toxicity. The current challenges in RT therefore comprise of better selection of patients who will benefit and lowering the dose to the organs at risk while maintaining the coverage of the actual microscopic spread. This thesis focuses on the definition and delineation of the CTV, on the geometrical uncertainties and their subsequent PTV margin, and on anatomical measures available for reducing dose to the organs at risk.

To start with the latter, a full bladder protocol, a belly board and IMRT can be used to reduce the exposure of small bowel. The clinical need of using all measures simultaneously is unknown. In chapter 2 we compare supine, prone and 2 different belly boards in the context of a full bladder protocol and IMRT to validate whether differences in positioning are clinically relevant.

Although IMRT has the ability to reduce the dose to the healthy tissue without compromising the PTV coverage [30, 31], the technique is not yet widely used for RT of rectal cancer for several reasons. First of all, the very conformal delivery of dose to the shape of the PTV with IMRT demands for accurate definition of the CTV, and adequate estimation of the PTV margin. A significant underestimation of the CTV or the PTV margin will result in a significant risk of under dosage with IMRT compared to less conformal techniques. Secondly, surgery is still regarded as the mainstay in rectal cancer. Introduction of IMRT in clinical practice is therefore more focused to tumor areas where RT is considered as the main treatment.

The first step to improve was the delineation of the CTV. There is an evidence based delineation atlas defining what should be delineated as CTV [27], but no studies are available that measured the reproducibility of CTV delineation among different radiation oncologists. In chapters 3 and 4 two studies on measuring and minimizing delineation variation in rectal cancer are presented.

Besides the variation in CTV delineation there is the CTV definition itself. In the evidence based delineation atlas [27], CTV definitions are differentiated for tumor location only, irrespective of TNM stage and possible involvement of the MRF, both well known factors for the development of LR. In chapter 5 we explored the possibility to further differentiate the CTV definition by incorporating these prognostic factors. For this study, a 3D analysis of the local recurrences of the Dutch TME trial was performed.
When the CTV is defined and delineated, a proper PTV margin should be added to cover uncertainties in setup variation, delineation variation and CTV shape variation. Of the 3 error sources, setup variation has been studied the most, but it is also the least significant and easiest to minimize using online or offline setup correction. For shape variation of the CTV there is almost no data available. Only Nuyttens et al. [49] described the variation of the anterior border of the CTV in ten, mostly post-operative, rectal cancer patients based on repeat CT data. Variation in the order of 1.0 cm SD indicated that shape variation is a major geometric uncertainty, and thus is important for the PTV margin. In chapters 6 to 8 more extensive 3D analysis of shape variation are described. In chapters 6 and 7 the mesorectal part of the CTV for early stage rectal cancer patients is analyzed retrospectively, based on available cone-beam CT (CBCT) data. In chapter 8 prospective repeat CT data for is used to describe the full 3D shape variation for the entire CTV for both early- and advanced stage rectal cancer.

Translation of the shape variation into a proper PTV margin is not obvious, as the well known margin recipes by Stroom et al. [50] and van Herk et al. [29] are both only applicable for rigid structures. In chapter 8 we described and validated a pragmatic approach to translate CTV shape variation into a PTV margin.

Finally there is the option to reduce required PTV margins by estimating the shape variation errors early during treatment and adapting the treatment plan accordingly. The possible margin reduction with this adaptive RT methodology and its effect on bowel dose was described in chapter 9 based on the repeat CT data from advanced rectal cancer patients.

The thesis is concluded with a general discussion (chapter 10) and an English and Dutch summary.
Introduction

References


Chapter 1


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