Brachytherapy for rectal cancer

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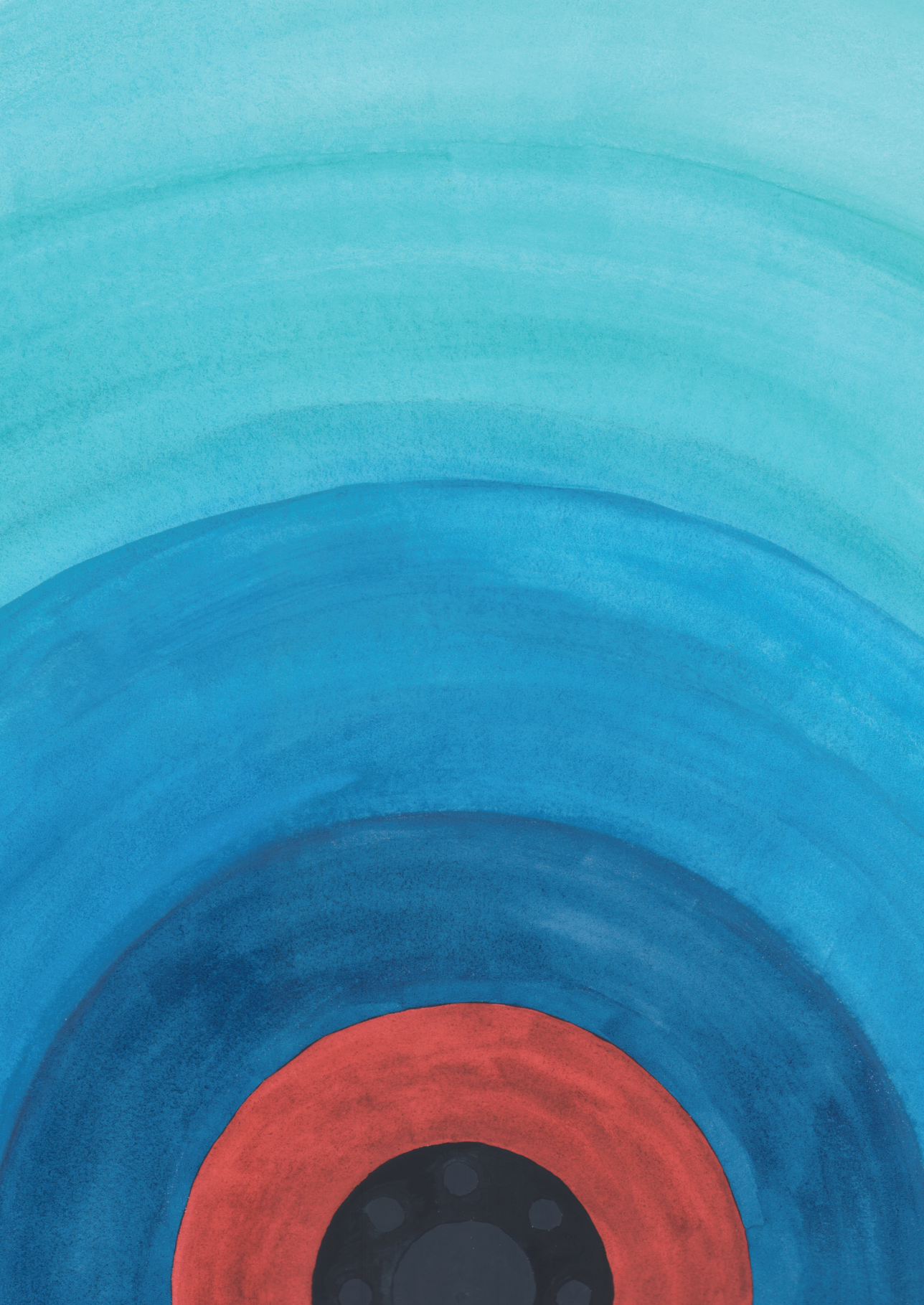

Chapter 1

Introduction and outline thesis

1. INTRODUCTION

1.1 Epidemiology

Colorectal cancer is the third most common cancer worldwide. One-third of all colorectal cancers are located in the rectum.[1,2] Rectal cancer is mainly observed in older patients with a median age of 70 years and approximately 30% being older than 75.[2,3] Figure 1 shows a clear increase in incidence in the past two decades, which is partly explained by aging of the population and partly by the introduction of a national screening program in 2014.[3,4] The proportion of patients that will be diagnosed in an early stage will likely rise due to nationwide screening.[5]

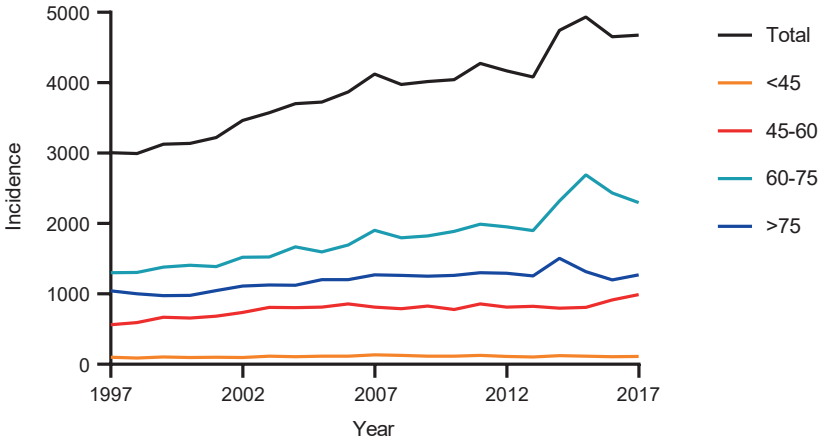

Figure 1. Netherlands Cancer Registry: incidence (total number of patients) and age distribution of rectal cancer in the Netherlands between 1997 and 2017.

1.2 Standard treatment

Standard treatment for non-metastasised rectal cancer is total mesorectal excision (TME). This resection technique was first described by Heald in 1982.[6,7] In the Netherlands, TME was implemented in the framework of the TME trial at the end of the 20th century. Nationwide, local recurrence rates improved from approximately 25% with blunt dissection to 11% with TME surgery.[8-11] Neoadjuvant radiotherapy further improves local control and two main schedules are accepted today as standard: Short course radiotherapy (SCRT) consisting of 5×5 Gy external beam radiotherapy and long course chemoradiotherapy (CRT) consisting of 25 fraction of 1.8-2.0 Gy with concurrent 5-fluorouracil or capecitabin.

Short course radiotherapy with immediate surgery was evaluated in three large randomised trials: the Swedish rectal cancer trial, the Dutch TME trial and the MRC CR07 trial. These trials showed that local recurrence is reduced by approximately 50%.[8,9,12] This resulted in a local

recurrence rate of 5% after 10 years in the TME trial. Although overall survival was not improved in the entire cohort, a subgroup analysis in patients with stage III rectal cancer with clear circumferential resection margins showed a significant increase in 10-year survival from 40% for patients undergoing TME surgery alone to 50% for patients treated with SCRT and TME surgery.[8] Neoadjuvant long course chemoradiotherapy (CRT) was investigated around the same time in several other trials with cT3-4/N+ tumours (EORTC 22921, FFCD 9203 and CAO/ARO/AIO-94). These showed superior local recurrance rates compared to neoadjuvant radiotherapy alone or postoperative chemoradiotherapy (6-8% vs. 13-16%).[13-17]

The results of aforementioned studies have led to differences in practice guidelines for neoadjuvant treatment around the world.[2,18,19] Current national guidelines in the Netherlands are displayed in Table 1.[19] Patients with early-stage rectal cancer have a low risk of local recurrence after TME surgery alone and currently no neoadjuvant radiotherapy is advised.[19] In patients with intermediate stage rectal cancer, SCRT is preferred over CRT because the former has a lower toxicity profile and comparable oncological outcomes.[20-22]

Recently, based on the results of the Stockholm III trial, SCRT with delayed surgery was introduced as an alternative to SCRT with immediate surgery. Delayed surgery is associated with increased downsizing and a reduced risk of postoperative complications compared to immediate surgery.[23] The increased burden of acute toxicity is the main disadvantage and both options can be discussed with patients with intermediate-risk rectal cancer.[24] In patients with risk factors for local recurrence (cT4, N2 or threatened mesorectal fascia), SCRT with immediate surgery is associated with a high rate of local recurrence (17%) and CRT with delayed surgery to allow for downstaging is preferred.[14,25] The effect of SCRT with delayed surgery in these high-risk patients has not been investigated but is considered as an alternative to CRT if patients are not fit enough for concurrent chemotherapy.

Table 1. Dutch guidelines for local treatment in rectal cancer

Risk group	TNM stage	Standard treatment
Very early	cT1 sm1 N0	Local excision
Early (good)	cT1-3bN0, MRF-	TME surgery
Intermediate (bad)	cT3c-dN0 / cT1-3N1, MRF-	SCRT+TME surgery
Advanced (ugly)	cT(x)MRF+/cT4/cN2	CRT + TME surgery

Abbreviations: MRF: distance to mesorectal fascia: MRF- > 1 mm, MRF+ < 1 mm; TME: total mesorectal excision; SCRT: short course radiotherapy (5×5 Gy); CRT: chemoradiotherapy (45-50 Gy, 1.8-2 Gy/fraction + oral capecitabine 825 to 1,000 mg/m2 bidaily)

The developments in the treatment of localised rectal cancer since the 1990s have improved the 5-year overall survival from 51% to 65%. While prognosis for stage I is very good with 94% 5-year overall survival, the survival of patients with stage II (cT3/4) and stage III (cN+) is still compromised by the increased risk of distant metastases with a 5-year overall survival of 77% in stage II and 65% in stage III.[26] In many countries, adjuvant chemotherapy is advised in

patients with high risk factors based on the beneficial effects of chemotherapy on recurrence and survival in colon cancer.[27,28] In rectal cancer, however, several trials have reported negative or inconclusive results and in the Netherlands, postoperative chemotherapy is therefore currently not advised.[29] Possible explanations for the absence of a survival benefit of chemotherapy are the poor compliance of postoperative chemotherapy and the interval between diagnosis and start of chemotherapy.

A potential solution to both problems is the administration of chemotherapy prior to surgery. This was the rationale for the international multicentre phase III Rapido study. Neoadjuvant SCRT followed by 6 or 9 courses of chemotherapy before TME was compared with standard neoadjuvant CRT and TME followed by postoperative chemotherapy according to local guidelines.[30] The primary endpoint was defined as Disease-related Treatment Failure (DrTF), including locoregional/distant failure, new colon carcinoma and treatment-related death. A recent presentation at the annual meeting of the American Society of Clinical Oncology demonstrated that DrTF was significantly improved in the experimental arm, with 23.7% at three years compared to 30.4% after standard CRT. Although acute toxicity was increased in the experimental arm (48% vs. 25%), the postoperative toxicity of adjuvant chemotherapy (37%) is avoided. Detailed analyses demonstrated no difference in long-term toxicity, overall health-related quality of life or low anterior resection syndrome score. It is likely that this new approach will be introduced in guidelines around the world for locally advanced rectal cancer.[30,31]

Morbidity of standard treatment

While oncological outcomes with these standardised treatments are excellent, they are associated with severe morbidity. TME surgery is associated with postoperative complications in approximately 40% of patients and sexual, urinary and bowel function is often compromised.[24,32-35] Symptoms of faecal incontinence, soiling, urgency, increased stool frequency, painful stools, emptying difficulties, altered consistency and unpredictable variation in bowel motions are often reported and are summarised as low anterior resection syndrome (LARS).[36,37] Neoadjuvant (chemo)radiotherapy further increases this risk of postoperative morbidity.[33,37,38]

1.3 Considerations for treatment adaptation in elderly patients

TME surgery

Risks of morbidity and postoperative mortality are substantially increased in frail elderly patients. Analyses from the Dutch TME trial and Comprehensive Cancer Centre registry up to 2002 showed high postoperative complication rates of 50% in patients over 75 years of age and increased 6-month mortality of 13.4% in patients aged 75 to 85, increasing to almost 30% in patients aged 85 to 95 years.[39] Especially elderly patients with comorbidities and a high American Society of Anaesthesiology (ASA) classification were at increased risk of postoperative mortality. Figure 2 shows the one-month postoperative mortality by age and ASA classification

from these analyses.[39] Since the TME trial, improvements in surgical and anaesthetic techniques, as well as the introduction of geriatric assessments, have contributed to a reduction of these risks in elderly patients.[40-43] A recent analysis of a prospective cohort showed that the rate of postoperative complications (38%) is no longer increased in patients older than 70 years.[44] The impact of postoperative complications on quality of life is, however, more pronounced in elderly patients compared to their younger counterparts. Equally important, postoperative mortality is still increased by 5.5% after 1 month and 14.8% at 1 year in patients over 75.[44-46]

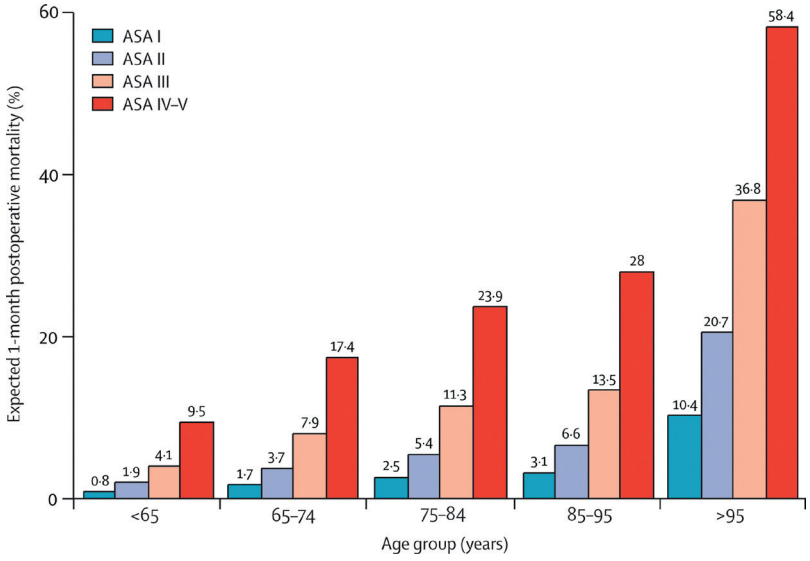

Figure 2. Expected 1-month postoperative mortality for a group of patients with stage 2 and stage 3 rectal cancer according to the Association of Coloproctology of Great Britain and Ireland score.*

Neoadjuvant (chemo)radiotherapy

Neoadjuvant (chemo)radiotherapy reduces the risk of local recurrence by approximately 50% (see Section 1.2 standard treatment). This improvement however comes at a cost of increased risk of complications and treatment morbidity. A subanalysis of the phase III ACCOR12/PRODIGE 2 study, which compared two chemoradiotherapy schedules (capecitabin/45Gy and capecitabin oxaliplatin/50Gy), further shows that elderly patients are at increased risk of severe acute toxicity compared to younger patients following the same regimen.[47] Also, the increase in postoperative complications (41% to 48%) and impact of bowel dysfunction

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on daily activities (22% to 34%), as observed in the TME trial, might be more relevant in frail patients than in fit patients.[32,44,48] Use of concurrent chemotherapy in long course radiotherapy is associated with a 4-fold increase in severe acute toxicity.[49]
In two randomised studies comparing CRT and SCRT, no difference in oncological outcome was observed. However, a favourable toxicity profile of SCRT was seen.[20,21,50] These observations demonstrate that, especially for frail patients, SCRT might be a good alternative to CRT. Alternatively, complete omission of the neoadjuvant treatment can be considered.[46,51] Data from a prospective colorectal cancer cohort between 2013 and 2016 indeed shows that elderly patients over 70 more often received SCRT with delayed surgery compared to younger patients (19% vs. 6%). Chemoradiotherapy was prescribed to 39% compared to 63% in younger patients and they were more likely to receive a permanent stoma (13% vs. 3%).[44]

Shared decision making based on geriatric assessment

Elderly rectal cancer patients represent a very heterogeneous group and a comprehensive geriatric assessment can be useful in guiding both physicians and patients in developing an integrated plan for care, treatment and follow-up. Comprehensive geriatric assessment is defined as a multidimensional, interdisciplinary diagnostic process focussing on an older cancer patient's medical, psychosocial and functional capacities. Patient's age is often less important than for example performance status and presence of comorbidities or geriatric syndromes.[42,43]
Two review articles provide an overview of considerations and treatment options in elderly patients with rectal cancer.[46,51] Wang et al. have composed a shared decision-making strategy which uses an algorithm for the management of the older cancer patient based on a comprehensive geriatric assessment by Balducci and Extermann:[51,52]

1) Fit patients: Patients who are functionally independent and have no serious comorbidity who may receive the full treatment.
2) Intermediate group: Patients in between the fit and frail groups, who may benefit from modified treatment with a lower toxicity profile.
3) Frail patients: Patients who are frail (dependence in one or more activities of daily living, three or more comorbid conditions, one or more geriatric syndromes), who are only candidates for palliative treatment.

Bujko et al. have developed a similar risk classification with four categories: (1) fit patients; (2) medium-fit patients, at surgical risk; (3) frail patients in whom radical surgery is contraindicated and (4) very frail patients. They provide several suggestions for radiotherapy adaptation for rectal cancer in each group. In the first two groups, adaptation of treatment volume and radiotherapy schedule is suggested, followed by surgical resection (either TME or local excision). For the third

group of frail patients, with a contraindication for surgery, a radical radiotherapy schedule is suggested as an alternative. And patients in the fourth group will likely be candidates for palliative radiotherapy alone.[46]

1.4 Radical radiotherapy

(Chemo)radiotherapy alone

As rectal cancer is a relatively radioresistant tumour, high doses are needed to achieve local control with radiotherapy alone.[53] To assess the chance of cure with radiotherapy alone (radical radiotherapy), the most reliable data can be extracted from surgical studies reporting the likelihood of a pathologic complete response (pCR) after neoadjuvant (chemo)radiotherapy. With standard dose fractionated external beam chemoradiotherapy (EBRT, 45-50 Gy in 1.8 Gy-2.0 Gy per fraction) a pCR is observed in approximately 16% of locally advanced tumours.[54,55] With dose escalation to 65 Gy or longer time until surgery, this number can be improved to 20-38%.[56-58] Furthermore, in early stages (cT1-3N0), the pCR rate is higher and the chance of cure with chemoradiotherapy alone is likely between 27-64%.[59-63]

In patients unfit for chemoradiotherapy, alternative schedules such as 5×5 Gy (SCRT), 13×3 Gy or 40-60 Gy in 2-4 Gy per fraction can be considered, but chances of a pathologic complete response are expected to be lower than with chemoradiotherapy.[64-66] Short course radiotherapy has resulted in a pCR rate of 10.4% in resectable tumours included in the Stockholm III trial.[23] Data from the Netherlands Cancer Registry show similar pCR rates of 9.3%.[67] Clinical T-stage was identified in this cohort as a significant predictor for tumour response and pCR rates decreased from 36.4% in cT1 tumours to 6.6% in cT4 tumours. In early stages a pCR with SCRT can be accomplished in around 32.2-35.9% based on two phase 2 studies in early rectal cancer using SCRT with local excision.[62,68]

Prior to the era of chemoradiotherapy, a schedule of 13×3 Gy external beam radiotherapy was used in two clinical trials in France. The Lyon 90-01 and 96-02 trials, performed in cT2-3 tumours, show a pCR rate of 7-15% after 13×3 Gy.[69,70] Wang et al. described the effect of long course radical radiotherapy in a retrospective cohort including all patients who received 40-60 Gy in 2-4 Gy per fraction. A clinical complete response was observed in 30%, but 78% developed a regrowth during follow-up resulting in a local control of only 6.6%.[64]

Dose escalation

In order to increase the chance of a complete response using radical radiotherapy, dose escalation is needed. Dose-response analyses indicate that doses as high as 92 Gy (equivalent dose in 2 Gy per fraction [EQD2]) are needed to achieve a complete pathologic response in 50% of patients (see Figure 3).[53] However, external beam doses higher than 50-65 Gy can result in

excessive toxicity and dose escalation to radiation doses > 80 Gy is currently only possible with an intraluminal radiotherapy boost. Two options are currently available: contact X-ray (CXB) and HDR endorectal brachytherapy (HDREBT).

There are only two randomised studies using these techniques: The first was the Lyon 96-02 study which aimed for increased sphincter preserving surgery after a CXB boost. Patients with a cT2-3Nx tumour received 13×3 Gy EBRT with 85 Gy CXB in three fractions. Surgery was performed 5 weeks after EBRT and a pCR rate of 35% and near pCR rate of 57% was observed.[70] The second study by Jakobsen et al. was designed to increase the chance of a pathologic complete response in cT3-4 tumours. Patients received 50.4 Gy chemoradiotherapy and were randomised to an HDR brachytherapy boost of 2×5 Gy or no boost. The major pathologic response rate was increased from 29% to 44%, but pCR was the same in both groups with 18%. This is probably the result of the large tumours included in this study and limited effect of the HDREBT boost on pathologic lymph nodes.[71] Several cohort studies have however shown more promising results for use of an intraluminal radiotherapy boost for organ preservation with complete responses up to 94%.[72-78]

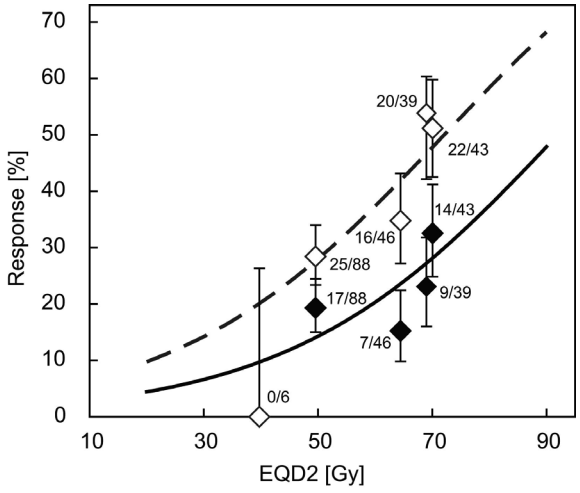

Figure 3. Dose-response relationships for complete and major response after preoperative chemoradiation therapy (CRT) for rectal cancer. Solid line, filled squares = pCR; dashed line, open squares = and major response (TRG1+2); Error bars indicate 68% confidence intervals. EQD2 = equivalent average dose to the tumour in 2-Gy fractions.*

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1.5 Intraluminal radiotherapy boost techniques

Contact X-ray (CXB)

Contact X-ray brachytherapy was developed in the 1930s in Germany as an alternative to radium brachytherapy in treatment of patients with cervical cancer and was further developed for rectal cancer in the 1950s by Professor Papillon in Lyon. Contact X-ray for rectal cancer (also referred to as the Papillon technique) delivers a very high dose to the rectal mucosa by using an X-ray tube with 50kV which is guided through a rigid rectoscope (see Figure 4.). The region irradiated is limited by the diameter of the rectoscope (max 3 cm) and the inverse square law. A surface dose of 100% will reduce to 50% at 6 mm and approximately one-third at 10 mm.[79,80] Dose is prescribed at the surface of the rectal tumour and is usually administered in 3-4 fractions of 20-30 Gy with a 2-week interval to allow for downsizing in between.[74]

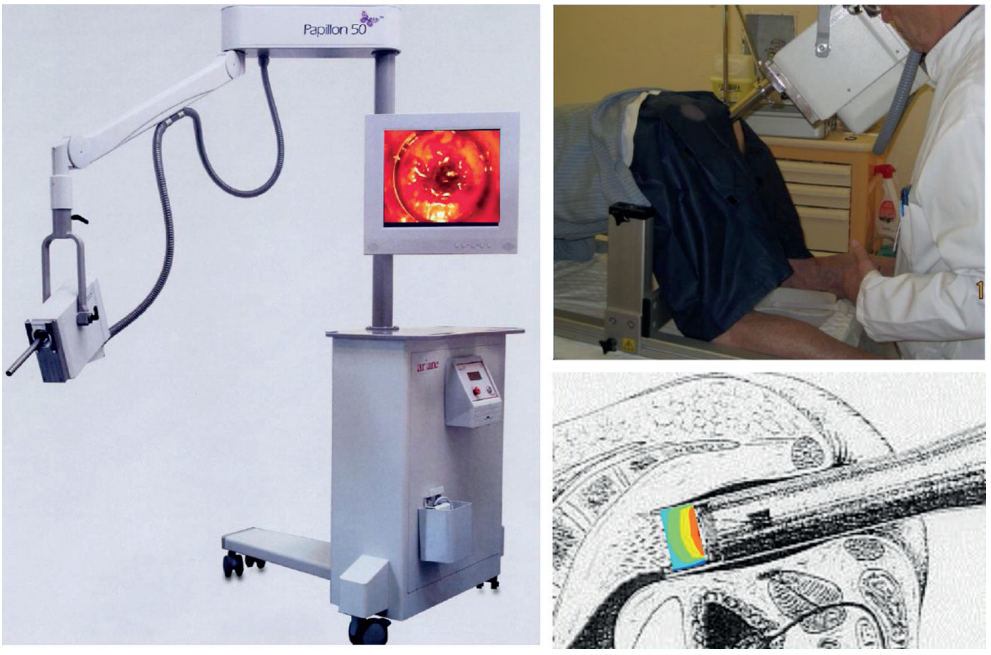

Figure 4. The Papillon 50 tm machine (Ariane Company UK, 2010). Irradiation of a rectal tumour with patient in knee-chest position. Dose display calculated with Monte Carlo showing the rapid fall off of the dose.*

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High dose rate endorectal brachytherapy (HDREBT)

The first reports on HDR brachytherapy for rectal cancer date back to 1988.[81,82] The development of high dose rate afterloading systems with relatively short treatment times made intraluminal brachytherapy for rectal cancers a realistic and practical option. Historically, there are two types of applicators developed for this purpose. The first is a rigid applicator with a central channel and optional shielding of 25-75% of the circumference. Positioning of this applicator is based on digital rectal examination or use of clips inserted during endoscopy and localisation of these clips with orthogonal X-rays. Dose is usually prescribed at 1 cm from the applicator surface and varies from 5-10 Gy per fraction.[76] This technique is mainly used in palliative care but has also been used as a boost to chemoradiotherapy in two dose-escalation trials initiated in Denmark.[71,75,76,83,84]

The second technique uses a flexible applicator with eight peripheral channels. It was developed by investigators of McGill University in Montreal for use in neoadjuvant radiotherapy. An inflatable semi-circular balloon is applied over the applicator, which is used to fixate the applicator within

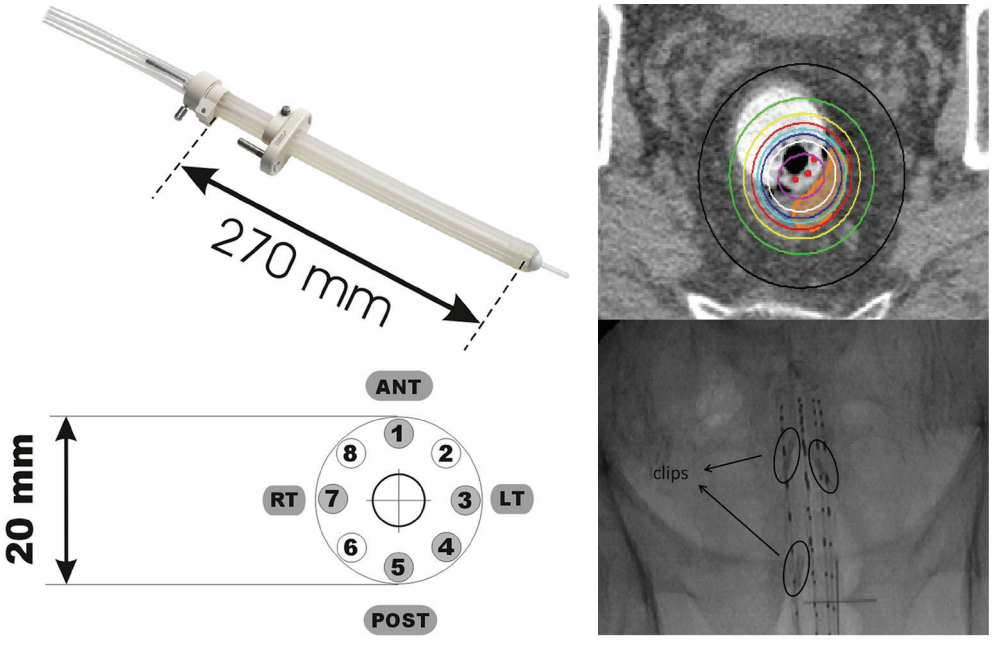

Figure 5. Left: Intracavitary mold applicator for HDR endoluminal brachytherapy (Elekta, Veenendaal); the bottom schematics represents the catheter positions. In catheter 1, 3, 4, 5 and 7, X-ray markers are placed.*
Right-top: axial slice of a planning CT and dose distribution. ● = active dwell position; isodose lines: Pink = 400%, Red 100%, Green 50% and Black 25% of prescribed dose.
Right-bottom: X-ray at time of treatment used for correction of rotation and depth of insertion.

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the rectal lumen and to divert the normal rectal mucosa on the contralateral wall. A CT scan is acquired with the applicator in situ and based on the diagnostic MRI and endoluminal clips placed during endoscopy, the tumour is delineated on the planning CT scan. Subsequently, a treatment plan with differential loading of the channels is constructed. The dose is prescribed at the radial margin of the tumour instead of a fixed distance from the applicator surface.[85,86] At time of treatment, adjustment of rotation and depth of insertion is accommodated by use of orthogonal X-rays with markers inserted in prespecified channels (see Figure 5). This image-guided technique allows for a more conformal dose distribution with increased sparing of normal tissue compared to a single channel catheter.[87]

Comparison of CXB and HDREBT

Both CXB and HDREBT have a steep dose gradient due to the inverse square law and are suitable for an endoluminal boost in radical radiotherapy. The techniques have never been formally compared, but CXB is preferred in small tumours because it results in a smaller irradiated volume due to complete shielding of tissue outside the circumference of the rigid proctoscope (see Figure 4 and 5). The clinical use of contact X-ray for rectal cancer is currently still limited because of the sparse availability of CXB machines, with only 11 machines in Europe (France, England, Switzerland, Sweden, Denmark, the Netherlands).[79] Important technical limitations are the restrictions in tumour size, accessibility of the tumour location with rigid endoscopy and the need for training of radiation oncologists in rigid rectoscopy. The volume that can be treated with HDREBT is much larger compared to CXB and is also not limited by the reach of rigid rectoscopy. Another advantage of the flexible applicator is that it is more comfortable for the patient than a rigid rectoscopy.

1.6 Rationale for the HERBERT study

The HERBERT study was initiated in 2007 by Professor Marijnen et al. to evaluate the feasibility of an HDR endorectal brachytherapy boost after external beam radiotherapy in elderly patients with rectal cancer who were unfit for chemotherapy or surgery. Because of the extensive experience in France with an internal CXB boost after 13×3 Gy, this schedule was selected for EBRT. The brachytherapy technique was adopted from the experience with neoadjuvant brachytherapy in Canada, as described above. In analogy with a brachytherapy boost in gynaecologic malignancies, a weekly brachytherapy schedule with three fractions was proposed. Because there were no data in the literature about the tolerability of a HDREBT boost, the study was designed as a brachytherapy boost dose escalation study which started with 3×5 Gy, six weeks after EBRT. Acute proctitis occurring within 6 weeks after brachytherapy was defined as dose-limiting toxicity and the primary endpoint was the maximum tolerated brachytherapy boost dose. Secondary aims were to evaluate the efficacy, toxicity and technique.

1.7 Aims and outlines of this thesis

In this thesis an alternative treatment option for frail or elderly patients with rectal cancer is evaluated. This treatment combines external beam radiotherapy with an endorectal brachytherapy boost and was evaluated in the HERBERT trial.

The basis of the treatment is external beam radiotherapy and the main limiting toxicity in external beam radiotherapy for rectal cancer is gastrointestinal toxicity. **Chapter 2** evaluates risk factors and dose-response relationships for gastrointestinal toxicity after chemoradiotherapy in patients with locally advanced rectal cancer. Three different methods for bowel contouring are compared and a review of the literature is performed to provide recommendations for dose constraints for small bowel loops and two commonly used alternative contours: bowelbag using EMBRACE guidelines and bowelbag using RTOG guidelines.

The primary outcome of the HERBERT trial is described in **Chapter 3**. Acute dose-limiting toxicity, clinical response to treatment, progression free- and overall survival and severe late toxicity are reported. **Chapter 4** provides a comprehensive overview of physician-reported, patient-reported and endoscopic toxicity. Further analyses on risk factors and dose-effect relationships for response and toxicity are provided in **Chapter 5.**

The technique used in the HERBERT study uses a single CT-based treatment plan for three brachytherapy fractions. A repeat CT side-study evaluates the added value of a CT-based adaptive approach in a subgroup of the HERBERT population. The results of this repeat CT study are described in **Chapter 6.** The next step in the optimisation of rectal brachytherapy will be MRI-guided brachytherapy. The REMARK study aims to select fiducial markers that are MRI compatible and can be used in MRI-guided radiotherapy for rectal cancer. **Chapter 7** describes the technical success rate and safety of implantation of four different gold fiducials in the rectal wall and the mesorectal fat in close proximity to the rectal tumour.

Chapter 8 provides a summary and **Chapter 9** a general discussion of the data presented in this thesis focussing on further development of endorectal brachytherapy and its use in treatment for rectal cancer.

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