Reducing uncertainties in image-guided radiotherapy of rectal cancer

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Chapter 1

Introduction

INTRODUCTION

Rectal cancer epidemiology

Worldwide, the incidence of colorectal cancer has increased in the last decade, especially in Western countries. This increase in incidence may be explained by modifiable lifestyle factors, such as smoking, alcohol intake, physical inactivity, obesity, low consumption of fruits and vegetables and high consumption of red meat and processed meat [1]. In addition, the introduction of population screening has contributed to an increased incidence. In the Netherlands, the incidence of colorectal cancer is one of the highest of all cancer types, with 15.306 new cases in 2016, of which 4461 were diagnosed as rectal cancer [2]. Since the early nineties, the incidence of rectal cancer has doubled and the 5-year survival has increased from 53% to 67% in recent years.

Survival of rectal cancer patients is mainly dependent on the disease stage at the time of diagnosis, with a better prognosis for early diagnosed patients. Unfortunately, most patients are unaware of their disease until clinical symptoms occur, with an already advanced stage as a result. In order to improve survival for colorectal cancer patients, population screening was introduced in the Netherlands in 2014. This has led to an increased incidence, leading to more early stage colorectal cancer patients at diagnosis. Apart from possibly less aggressive treatment in some patients, improved overall survival of colorectal cancer patients has been anticipated [3].

Treatment

Surgery

Treatment advances in the last decades have led to improved local control and overall survival of rectal cancer patients. Surgery is the mainstay of treatment and a major step in surgical quality was made with the introduction of standardized total mesorectal excision (TME) surgery by Heald [4]. In a TME procedure, the entire mesorectal compartment is excised along anatomical planes. The specimen includes the rectum, surrounding mesorectum and perirectal lymph nodes, enclosed by the mesorectal fascia (MRF). The introduction of this standardized technique reduced local recurrence rates from over 25% to approximately 10% [4–6].

Generally, two approaches of TME surgery are used. An abdominoperineal resection (APR) is generally used in patients with low lying tumors and involves removal of the anus, rectum and part of the sigmoid colon along with the complete mesorectum. Due to the removal of the anal sphincter complex, an APR always results in a permanent stoma. A low anterior resection (LAR) involves removal of the part of the rectum in which the tumor is located along with the surrounding mesorectum. An anastomosis is then performed to attach the colon to the remaining part of the rectum. To reduce the risk of anastomotic leakage, patients may have a temporary stoma, which can be reverted later on [7].

For early stage rectal cancer patients with T1N0, an alternative to TME surgery might be a local excision. In this procedure, the tumor is locally excised through the anus using transanal endoscopic microsurgery (TEM), thereby saving the rectum and sphincter complex. Local excision surgery is associated with lower morbidity and mortality rates compared to TME surgery [8]. However, TEM has an increased risk of a non-radical resection [9] as well as a risk of leaving involved lymph nodes behind. As a result, local recurrence rates are substantially higher after TEM compared to TME [10].

(Chemo)radiotherapy

For more advanced cases, the addition of (chemo)radiotherapy to TME surgery further reduced local recurrence rates to 5-8% [11–14]. Two general treatment schedules are used as a neoadjuvant treatment. For intermediate risk patients, i.e. cT1-3N1 or cT3N0 with >5 mm extramural invasion and no involved mesorectal fascia (MRF), short-course radiotherapy (SC-RT) is given with 25 Gy in 5 fractions within one week in northern European countries.

The MRF is the resection plane of a TME resection and involvement of the MRF leads to positive circumferential resection margins (CRM) in a large number of patients. Several studies have demonstrated an increased local and distant recurrence risk after resections with a positive CRM [15]. If the distance of the primary tumor or involved lymph node to the MRF is smaller than or equal to 1 mm, it is considered an involved MRF and the patient is not eligible for direct TME surgery. For high risk patients, being cT4, cT3 with involved MRF, and/or cN2 or extramesorectal pathological nodes, long-course chemoradiotherapy (LC-CRT) is given with 45-50 Gy in fractions of 1.8-2 Gy.

The addition of preoperative SC-RT in stage I-III patients has been investigated in the TME trial and the MRC CR07 trial. In the TME trial, patients with resectable rectal cancer were randomized between SC-RT followed by immediate surgery or surgery alone [11]. In the MRC CR07 trial, patients with resectable rectal cancer were randomized between SC-RT with direct TME surgery or TME surgery with selective adjuvant chemoradiotherapy [14]. In both trials, a significant reduction in local recurrence rate was observed in patients with a negative CRM after TME in the radiotherapy group compared to the TME alone group. Because of the short interval between radiotherapy and TME surgery, no downstaging was observed [16].

The addition of chemotherapy to radiotherapy was investigated in the FFCD 9203 and EORTC 22921 trials. In the EORTC 22921 trial, patients with resectable, T3-T4 rectal cancer were randomized between preoperative long-course radiotherapy with or without fluorouracil based chemotherapy. In addition, the role of adjuvant chemotherapy was investigated, resulting in a 2x2 design [12]. In the FFCD 9203 trial, patients with resectable T3-4 rectal cancer were randomized between preoperative long-course radiotherapy with or without concomitant chemotherapy [17]. Time between (chemo)radiotherapy and surgery was 3-10 weeks. In both trials, the addition of chemotherapy resulted in lower local recurrence rates compared to long-course radiotherapy only. Ten year local recurrence was 22.4% vs 11.8% in the

EORTC 22921 trial and 5-year local recurrence was 16.5% vs 8.1% in the FFCD 9203 trial. In addition, more tumor downstaging was observed in the chemoradiotherapy group.

The Stockholm III trial investigated the optimal fractionation of neoadjuvant radiotherapy and timing to surgery by randomizing patients with resectable rectal cancer between short-course radiotherapy with immediate surgery, short-course radiotherapy with delayed surgery and chemoradiotherapy with delayed surgery. Interim analyses showed that patients in the SC-RT with delayed surgery group had a greater degree of tumor regression and a higher pathological complete response rate compared to the SC-RT with immediate surgery group [18,19]. After a follow-up of a minimum of 2 years, no differences in local recurrences, distal recurrences and overall survival were observed. In addition, the risk of surgical complications was lower in the delayed surgery groups. Preoperative toxicity was however higher.

Frail patients that are considered unfit for surgery are usually also unfit for chemotherapy. For these patients, definitive radiotherapy can be offered. Literature describes varying schedules and techniques, including external beam radiotherapy (EBRT), contact therapy and brachytherapy [20].

Toxicity and complications

The introduction of standardized TME surgery led to a substantial reduction in local recurrence rates. However, after TME surgery a permanent stoma is required in about 10-20% of cases and a temporary stoma is required in 60-70% of cases of which many are not reversed [21,22]. In addition, TME surgery can result in substantial morbidity, including bowel leaks (16%), urinary incontinence or retention (25-34%), sexual dysfunction, and daily symptoms of urgency, incomplete emptying and stool frequency (30-40%) [23–27]. Thirty-days operative mortality is around 3-6% for patients <75 years of age and around 10-14% for patients >75 years of age [28].

While pre-operative (chemo)radiotherapy reduced local recurrence rates, it is also associated with an increased risk of side effects such as bowel and sexual dysfunction [29]. In the TME trial, 10-year local recurrence rates were lower in the radiotherapy group (5% vs 11%, $p<0.0001$), but no benefit in overall survival was observed (48% vs 49%). In a subgroup analysis, a benefit in overall survival was observed in the radiotherapy group in TNM stage III patients (50% vs 40%) with negative CRM. However, in TNM stage I and II patients, overall survival was lower in the radiotherapy group (65 vs 72% for stage I and 51 vs 57% for stage II) [11]. Although one has to be careful with interpretation of unplanned subgroup analyses, these results seem to suggest that EBRT can cause a systemic effect. It has to be noted that patients in the TME trial were treated with a box technique with conventional 2D treatment planning, which may have contributed to the systemic effect. The results also show that patient selection based on disease stage could be useful, as overall survival was lower in stage I-II rectal cancer patients in the SC-RT group. In addition, reducing the integral dose and/or the dose to the organs at risk may reduce the side-effects associated with radiotherapy.

Reducing treatment related toxicity and morbidity

Improvements in the treatment of rectal cancer patients have led to increased survival. As a result, long-term outcome has become an increasingly important factor. In addition, the introduction of population screening will lead to earlier detection of the disease with probably improved survival as a result [3]. Both preoperative (chemo)radiotherapy and TME surgery are associated with toxicity and complications. As a result, research for rectal cancer treatment has focused on the reduction of radiation dose to (healthy) tissue and less extensive surgery or omission of surgery in selected patients.

Neoadjuvant radiotherapy

The target volume for neoadjuvant radiotherapy for rectal cancer typically encompasses the primary tumor, with elective irradiation of the whole mesorectum and presacral and internal iliac nodes, with the cranial border around the level of the sacral promontory and the caudal border at least 2 cm below the primary tumor. The most important organs at risk are the small bowel and the sphincter complex. Due to the large target volume and the proximity of these organs at risk to the target volume, dose is deposited in these organs at risk which causes part of the radiotherapy treatment related toxicity. In addition, dose deposition in nerves located in the pelvis may attribute to decreased functional outcome.

Reduction of dose to healthy tissue can be achieved by decreasing treatment margins, or by using an alternative treatment technique. Research on the interfraction displacement of the CTV resulted in guidelines on required margins for rectal cancer radiotherapy. These required margins reduced the PTV volumes on average with 16% (SC-RT) and 24% (LC-CRT) compared to previous standard practice [30].

EBRT is currently the standard treatment modality for neoadjuvant radiotherapy for rectal cancer. With EBRT, the patient is irradiated using an external beam, in which radiation dose is deposited in the healthy tissue surrounding the target volume before it reaches the target volume. An attractive alternative treatment technique is intracavitary irradiation, that offers the advantage of delivering a high dose to the tumor from the inside while sparing surrounding organs at risk due to a steep dose gradient. Intracavitary irradiation for rectal cancer is an experimental and specialized treatment technique that is not widely available. It can be applied using either contact therapy or brachytherapy. Contact therapy is performed using a 50 kV handheld tube under direct visual control of the tumor [31]. Due to the low energy and therefore a steep dose fall-off, a very localized treatment can be applied. Brachytherapy can be given endoluminally, with an applicator inserted in the rectum. A number of different rectal applicators are available, ranging from single channel rigid applicators to flexible multichannel applicators [32]. With an afterloading system, an irradiation source can be guided through the channels in order to irradiate the region of interest. The multichannel flexible applicator is often used for high-dose rate endorectal brachytherapy (HDREBT) and has the advantage that the eight channels are placed circumferential near the edge of the applicator, which allows conformal treatment planning by using the channels that are located near the tumor. Although HDREBT is an invasive procedure as opposed to EBRT, it is well tolerated by most patients [33].

Compared to the target volume in neoadjuvant EBRT, brachytherapy reduces the irradiated volume considerably, leading to less dose to normal tissue. In addition, the dose in the tumor itself is significantly higher. However, potential positive lymph nodes that are further away from the tumor are not irradiated or receive a lower dose compared to EBRT. Nonetheless, the role of HDREBT as a neoadjuvant treatment was demonstrated by the group of Vuong *et al*. In a single center study, neoadjuvant HDREBT (4x 6.5 Gy) was given for mainly T3 tumors (88.8%) with 34% of patients having N+. A final pathologic stage of TONO-2 was reached in 27% and 5-year local control was 95% [34]. In a recent retrospective chart review that compared HDREBT to EBRT (mainly chemoradiotherapy), pathological complete response rates were similar (18.8% in the HDREBT group vs 17.1% in the EBRT group) and T-stage downstaging was significantly higher in the HDREBT group (59.4% vs 28.5%, p<0.01) [35]. Hesselager *et al.* performed a matched comparison of 318 patients treated with preoperative HDREBT (4x 6.5 Gy, TME after 4-8 weeks), preoperative SC-RT (5x5 Gy, direct TME) and TME only [36]. Less perioperative bleeding was reported in the HDREBT group compared to the SC-RT and TME only group (380 mL, 947 mL and 919 mL, respectively). In addition, less re-interventions were performed in the HDREBT group than in the SC-RT and TME only group (4.1%, 14.2% and 12.3%, respectively). Although it was not the primary endpoint of the study, a pathological complete response rate of 23.6% was reported after HDREBT. However, it is difficult to draw firm conclusions based on these non-randomized trials.

Organ preservation

The reported negative effects of rectal cancer surgery led to increased interest for organ preservation, in which surgery might be omitted if the patient experiences a complete response after neoadjuvant therapy. In these patients, a 'watch and wait' strategy with omission of surgery and a strict follow-up protocol seems to be a safe alternative to surgery [37]. Surgery and the related morbidy and mortality are then avoided.

A pathological complete response (pCR) is observed in 15-25% of patients after standard chemoradiotherapy [38,39]. Complete response rates up to 50% are observed in centers with a dedicated watch and wait protocol, probably due to better patient selection [40,41]. Complete response rates might be increased by delivering a higher dose to the tumor [42,43]. This may therefore be beneficial in organ preservation strategies in order to increase the chance of a complete response. Tumor dose can be increased by applying a boost using EBRT or intracavitary irradiation.

A randomized trial comparing 13x3 Gy radiotherapy with or without an endocavitary boost using X-ray contact therapy (85 Gy in 3 fractions) reported an improved clinical complete response rate (24% vs 2%) in the boost group [44]. No difference in local relapse and acute or postoperative toxicity were reported and 2-year overall survival was similar. Another randomized trial compared LC-CRT (28 x 1.8 Gy) with- or without HDREBT boost (2 x 5 Gy) in resectable T3 and T4 rectal cancer patients [45]. The R0 resection rate was higher in the boost group (99% vs 90%) as was the major response rate defined as tumor regression grade 1 and 2 (44% vs 29%). No difference was found in toxicity or surgical

complications. Unfortunately, no difference in pCR rate was reported. The HERBERT trial was a dose escalation trial in which a HDREBT boost in 3 weekly fraction of 5-8 Gy was applied after 13 x 3 Gy EBRT in inoperable and elderly patients [46]. The maximum tolerated dose was determined at 7 Gy. Overall, a CR rate of 60% was observed. However, the treatment came with substantial risk of toxicity, with 40% grade ≥3 proctitis.

In order to facilitate organ preservation in early stage rectal cancer patients, (chemo)radiotherapy has to be given in order to control the tumor. This group of patients would normally not receive neoadjuvant treatment as the standard of care for these patients is TME surgery. The risk of pelvic lymph node involvement or distal mesorectal nodal involvement is very low in early rectal cancer patients. Therefore, it is doubtful whether the typically used large target volumes are required for these patients and reduction of the target volume to only include the peritumoral region of the primary tumor and mesorectum seems reasonable. The significant volume reduction might lead to decreased treatment-related toxicity without compromising oncological outcome. This is currently being investigated in the STAR-TReC trial, which assesses the feasibility of short-course radiotherapy or long-course chemoradiotherapy with subsequent two-stage response assessment as an alternative to TME surgery. Patients with T1-3bN0M0 rectal cancer are randomized between TME, organ preservation utilizing LC-CRT and organ preservation utilizing SC-RT. The radiotherapy target volume only includes the mesorectum [47].

Treatment delivery techniques

In order to deliver radiotherapy safely, a target volume needs to be defined to steer the treatment planning. In general, three target volumes are defined: the gross tumor volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV). The GTV is defined as macroscopic tumor tissue which can be seen, palpated or imaged. The CTV is defined as the GTV plus the volume that is expected to contain any microscopic tumor deposits. Since microscopic tumor deposits in the tissue surrounding the tumor cannot be imaged, guidelines have been developed for delineation of the CTV for rectal cancer based on local recurrence patterns in the pelvis [48].

To ensure full coverage of the CTV by the prescribed dose, geometrical deviations of the treatment process should be taken into account. These deviations for example include CTV delineation errors, setup errors of the patient with respect to the treatment machine, and inter- and intrafraction CTV motion. Geometrical deviations are separated into two components: treatment preparation (systematic errors) and treatment execution (random errors). Systematic errors result in a shift of the dose distribution with respect to the target volume, while random errors result in blurring of the dose distribution [49]. The geometrical deviations are taken into account by adding a PTV margin to the CTV. Increasing the margin size will increase the chance that the CTV receives full coverage by the prescribed dose. However, with increasing margin size, more healthy tissue will be irradiated with risk of side-effects.

Image-guided external beam radiotherapy

EBRT delivery techniques have evolved in the past decades to deliver radiation doses with increasing conformality. During the mid-nineties, a box technique was commonly used. It utilizes multiple (e.g. 3 or 4) rectangular beams, aimed at the target at any angle in the transverse plane. Each beam was homogeneous in terms of intensity. This technique was replaced by 3D conformal radiotherapy. Using a multileaf collimator, the shape of each beam could be adapted to the shape of the PTV. A more conformal approach is intensity-modulated radiotherapy (IMRT), in which each beam is divided into segments. The beam intensity can be varied individually for each segment, resulting in more conformal treatment plans with a more homogeneous dose distribution within the PTV compared to the more conventional delivery techniques [50,51]. IMRT can also be delivered with a rotating gantry, in which rotation speed and beam intensity can be modulated, called volumetric arc therapy. Each improvement in radiotherapy delivery technique led to more conformal treatment plans, with higher dose gradients at the edges of the target volume. As a result, the treatment plans will be less forgiving in terms of geometrical deviations. Small deviations can lead to underdosage of the target volume if insufficient margins are used as the target volume will move out of the high dose region.

In image-guided radiotherapy (IGRT), corrections are applied based on measurements of the geometrical deviations. The imaging devices that are used to measure the geometrical deviations have evolved in the past years. In the nineties, an electronic portal imaging device (EPID) was used to acquire 2D projection images by measuring the exit dose [52]. The bony anatomy of the patient could be visualized and the position of the bony anatomy with respect to the treatment field could be corrected to match that of the treatment plan, if necessary.

New imaging modalities that could be used for setup correction were introduced in the last decade, including in-room CT, kV-CBCT on a linear accelerator and MV-CT on a helical radiotherapy unit. All these modalities have in common that they could perform three-dimensional (3D) imaging of the patient on the treatment table. However, the soft tissue contrast of these modalities is limited, which makes setup correction based on any other tissue than bony anatomy challenging [53]. In a GTV boost setting, setup correction can therefore not be performed on the GTV itself. As an alternative, fiducial markers could be used as a surrogate for the GTV. Fiducials have been used for setup correction of the target volume in prostate cancer and esophageal cancer [54,55]. The most recent advancement in onboard imaging is the MR-guided radiotherapy system [56]. With the superior soft tissue contrast of MRI, setup correction could be performed based on a direct visualization of the GTV. However, MR-guided radiotherapy systems are not widely available yet.

With increased interest for organ preservation and GTV dose escalation, improvements aimed at boost delivery for rectal cancer are timely. Although extensive research has been performed on the inter- and intrafraction displacement of the CTV relative to the bony anatomy, limited research was performed on the inter- and intrafraction displacement of the GTV relative to bony anatomy to determine margins for

a GTV boost [57–59]. As a result, a wide range of clinically used PTV margins of 7-30 mm is described in literature [60–64].

Setup correction could potentially be performed based on the fiducials instead of bony anatomy. To do so, the fiducials need to be representative of the GTV and the fiducials should be visible on MRI to accurately determine the fiducial-GTV spatial relationship. Literature on the use of fiducials in rectal cancer patients focuses on insertion technique, retention rate and complications [65,66]. The stability of fiducials with respect to the GTV has not been investigated. MRI visibility of fiducials has been evaluated in phantoms, but no in-vivo analysis has been reported [67,68].

Image-guided brachytherapy

The HDREBT procedure using the flexible multichannel applicator has been described first by Vuong *et al.* [69]. During endoscopy, the length and size of the tumor is assessed and endoluminal clips are attached to the rectal wall near the tumor to be able to visualize the tumor extent on radiographs for position verification. The target volume and endoluminal clips are delineated on a planning CT scan with applicator in situ and the applicator is reconstructed, which means that the position of the eight catheter channels in the applicator are denoted on the CT scan. Before irradiation, position verification of the applicator is performed. Dummy catheters containing tungsten markers that can be visualized on a radiograph are inserted into three channels of the applicator. Subsequently, anterior-posterior and lateral radiographs are acquired of the patient with applicator in situ. The position of the endoluminal clips and tungsten markers are used to check the insertion depth and rotation of the applicator. If the applicator is positioned correctly, irradiation is initiated.

Due to the steep dose gradient of HDREBT, interfractional anatomical variations of millimetres can have a substantial impact on dose to the target volume or organs at risk. Most publications on the use of HDREBT describe oncological outcomes, but do not report on the technical aspects of the brachytherapy procedure [70–72]. Initial publications describe a procedure using a single planning CT scan for all subsequent fractions [69,73]. More recent publications describe a more adaptive approach, acquiring a planning CT scan at each fraction [74,75]. So far, the possible dosimetric benefit of using an adaptive approach has not been reported.

HDREBT treatment planning is currently performed using a planning CT, on which accurate localization of the tumor is difficult due to limited soft tissue contrast. MRI could be used to accurately determine the tumor location due to its superior soft tissue contrast [76]. Given that the endoluminal clips that are used for position verification create large artifacts on MRI [77], alternative MRI-compatible fiducial markers may be used. However, similar to the potential application of fiducial markers in an EBRT boost, the visibility on MRI and the stability with respect to the GTV has not been investigated.

A further improvement in the HDREBT procedure would be to omit the planning CT scan and perform delineation and treatment planning on MRI only. MRI-only brachytherapy is already the standard for brachytherapy of cervical cancer [78]. Reconstruction of the rigid applicator is performed by rigidly registering a model of the applicator to the applicator on the MRI scan. However, such an approach is not available for the flexible rectum applicator. In addition, the applicator causes a signal void on the currently used anatomical sequences and the individual channels cannot be identified. Therefore, the challenge in MRI-only HDREBT lies in the reconstruction of the flexible applicator on MRI.

Thesis outline

As described, both TME surgery and radiotherapy are associated with increased risk of side-effects. As a result, research is focused on increasing the dose to the tumor to achieve higher response rates for possible organ preservation and on the reduction of irradiated (healthy) tissue. The purpose of this thesis is to reduce uncertainties in image-guided radiotherapy of rectal cancer to increase the accuracy of external beam radiotherapy boosting and high-dose rate endorectal brachytherapy.

Initial publications on HDREBT for rectal cancer describe the use of a single planning CT for all subsequent fractions, while more recent literature describes a procedure using a planning CT at each fraction. However, a dosimetric comparison between the two approaches has not been performed to date. The question is whether the increased patient burden of a planning CT scan at each fraction is justified by any dosimetric improvement in terms of target volume coverage and dose to organs at risk. **Chapter 2** describes the difference between the two approaches in terms of target volume coverage and dose to the organs at risk.

MRI-compatible fiducial markers can be used for HDREBT as an alternative to the endoluminal clips. This would allow the use of MRI for treatment planning for HDREBT. For EBRT, setup correction based on fiducial markers could potentially increase the accuracy of a GTV boost compared to setup correction on bony anatomy. To accomplish this, the fiducial markers need to be visible on MRI to determine the spatial relationship between fiducials markers and the GTV. **Chapter 3** evaluates the MRI visibility of four different gold fiducial markers.

To enable MRI-only planning for HDREBT, the applicator and the individual channels need to be visible on MRI. However, the applicator creates a signal void on currently used anatomical MRI sequences. **Chapter 4** investigates whether an ultrashort echo time sequence can be used to visualize the individual channels within the applicator and reports on the geometric fidelity.

To use fiducials as a surrogate for the GTV, the stability of the fiducials with respect to the GTV needs to be determined. In **Chapter 5**, the stability of implanted gold fiducial markers relative to the GTV is determined. Furthermore, the inter- and intrafraction displacement of the GTV is characterized and required margins for different setup correction scenarios in a EBRT GTV boost setting are suggested.

In the STAR-TReC trial, a novel target volume is used which includes only the mesorectum. Mesorectum only planning is intended for early stage rectal cancer with the aim of reducing the CTV and thereby reducing dose to the healthy tissue while maintaining local control. **Chapter 6** describes the results of a quality assurance program for mesorectum only planning.

REFERENCES

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683–91.
2. Nederlandse Kankerregistratie (NKR), IKNL 2019.
3. Morris EJA, Whitehouse LE, Farrell T, Nickerson C, Thomas JD, Quirke P, *et al.* A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. *Br J Cancer* 2012;107:757–64.
4. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;1:1479–82.
5. Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, Van Houwelingen HC, *et al.* Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: An international analysis of 1411 patients. *Eur J Surg Oncol* 1999;25:368–74.
6. Ridgway PF, Darzi AW. The Role of Total Mesorectal Excision in the Management of Rectal Cancer. *Cancer Control* 2003;10:205–11.
7. Bakker IS, Snijders HS, Wouters MW, Havenga K, Tollenaar RAEM, Wiggers T, *et al.* High complication rate after low anterior resection for mid and high rectal cancer; results of a population-based study. *Eur J Surg Oncol* 2014;40:692–8.
8. Restivo A, Zorcolo L, D'Alia G, Cocco F, Cossu A, Scintu F, *et al.* Risk of complications and long-term functional alterations after local excision of rectal tumors with transanal endoscopic microsurgery (TEM). *Int J Colorectal Dis* 2016;31:257–66.
9. Endreseth BH, Myrvold HE, Romundstad P, Hestvik UE, Bjerkeset T, Wibe A, *et al.* Transanal excision vs. major surgery for T1 rectal cancer. *Dis Colon Rectum* 2005;48:1380–8.
10. De Graaf EJR, Doornebosch PG, Tollenaar RAEM, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, *et al.* Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. *Eur J Surg Oncol* 2009;35:1280–5.
11. Van Gijn W, Marijnen CAM, Nagtegaal ID, Kranenbarg EMK, Putter H, Wiggers T, *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;12:575–82.
12. Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, *et al.* Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: Long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014;15:184–90.
13. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, *et al.* Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;30:1926–33.
14. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, *et al.* Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009;373:811–20.
15. Nagtegaal ID, Quirke P. What Is the Role for the Circumferential Margin in the Modern Treatment of Rectal Cancer? *J Clin Oncol* 2008;26:303–12.
16. Marijnen CAM, Nagtegaal ID, Klein Kranenbarg E, Hermans J, Van de Velde CJH, Leer JWH, *et al.* No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001;19:1976–84.

17. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, *et al.* Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *J Clin Oncol* 2006;24:4620–5.

18. Pettersson D, Cederniark B, Holm T, Radu C, Pahhnan L, Glimelius B, *et al.* Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. *Br J Surg* 2010;97:580–7.

19. Pettersson D, Lörinc E, Holm T, Iversen H, Cedermark B, Glimelius B, *et al.* Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer. *Br J Surg* 2015;102:972–8.

20. Wang SJ, Hathout L, Malhotra U, Maloney-Patel N, Kilic S, Poplin E, *et al.* Decision-Making Strategy for Rectal Cancer Management Using Radiation Therapy for Elderly or Comorbid Patients. *Int J Radiat Oncol Biol Phys* 2018;100:926–44.

21. Anderin K, Gustafsson UO, Thorell A, Nygren J. The effect of diverting stoma on long-term morbidity and risk for permanent stoma after low anterior resection for rectal cancer. *Eur J Surg Oncol* 2016;42:788–93.

22. Kim MJ, Kim YS, Park SC, Sohn DK, Kim DY, Chang HJ, *et al.* Risk factors for permanent stoma after rectal cancer surgery with temporary ileostomy. *Surg (United States)* 2016;159:721–7.

23. Marijnen CAM, Kapiteijn E, van de Velde CJH, Martijn H, Steup WH, Wiggers T, *et al.* Acute Side Effects and Complications After Short-Term Preoperative Radiotherapy Combined With Total Mesorectal Excision in Primary Rectal Cancer: Report of a Multicenter Randomized Trial. *J Clin Oncol* 2002;20:817–25.

24. Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ, *et al.* Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Ann Surg* 2005;242:212–23.

25. Wallner C, Lange MM, Bonsing BA, Maas CP, Wallace CN, Dabhoiwala NF, *et al.* Causes of fecal and urinary incontinence after total mesorectal excision for rectal cancer based on cadaveric surgery: A study from the cooperative clinical investigators of the Dutch total mesorectal excision trial. *J Clin Oncol* 2008;26:4466–72.

26. Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Hölzel D, *et al.* Quality of Life in Rectal Cancer Patients: A Four-Year Prospective Study. *Ann Surg* 2003;238:203–13.

27. Temple LK, Bacik J, Savatta SG, Gottesman L, Paty PB, Weiser MR, *et al.* The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. *Dis Colon Rectum* 2005;48:1353–65.

28. Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: Prospective national study. *Br Med J* 2003;327:1196–9.

29. Wiltink LM, Chen TYT, Nout RA, Meershoek-Klein Kranenbarg E, Fiocco M, Laurberg S, *et al.* Health-related quality of life 14years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomised trial. *Eur J Cancer* 2014;50:2390–8.

30. Nijkamp J, Swellengrebel M, Hollmann B, De Jong R, Marijnen C, Van Vliet-Vroegindeweij C, *et al.* Repeat CT assessed CTV variation and PTV margins for short- and long-course pre-operative RT of rectal cancer. *Radiother Oncol* 2012;102:399–405.

31. Gérard JP, Myint AS, Croce O, Lindegaard J, Jensen A, Myerson R, *et al.* Renaissance of contact x-ray therapy for treating rectal cancer. *Expert Rev Med Devices* 2011;8:483–92.

32. Myint AS. Novel radiation techniques for rectal cancer. *J Gastrointest Oncol* 2014;5:212–7.

33. Néron S, Perez S, Benc R, Bellman A, Rosberger Z, Vuong T. The experience of pain and anxiety in rectal cancer patients during high-dose-rate brachytherapy. *Curr Oncol* 2014;21:89–95.

34. Vuong T, Richard C, Niazi T, Liberman S, Letellier F, Morin N, *et al.* High dose rate endorectal brachytherapy for patients with curable rectal cancer. *Semin Colon Rectal Surg* 2010;21:115–9.

35. Garfinkle R, Lachance S, Vuong T, Mikhail A, Pelsser V, Gologan A, *et al.* Is the pathologic response of T3 rectal cancer to high-dose-rate endorectal brachytherapy comparable to external beam radiotherapy? *Dis Colon Rectum* 2019;62:294–301.

36. Hesselager C, Vuong T, Påhlman L, Richard C, Liberman S, Letellier F, *et al.* Short-term outcome after neoadjuvant high-dose-rate endorectal brachytherapy or short-course external beam radiotherapy in resectable rectal cancer. *Color Dis* 2013;15:662–6.

37. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, *et al.* Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018;391:2537–45.

38. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, *et al.* Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. *Lancet Oncol* 2010;11:835–44.

39. Sanghera P, Wong DWY, McConkey CC, Geh JI, Hartley A. Chemoradiotherapy for Rectal Cancer: An Updated Analysis of Factors Affecting Pathological Response. *Clin Oncol* 2008;20:176–83.

40. Maas M, Lambregts DMJ, Nelemans PJ, Heijnen LA, Martens MH, Leijtens JWA, *et al.* Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. *Ann Surg Oncol* 2015;22:3873–80.

41. Habr-Gama A, Gama-Rodrigues J, São Julião GP, Proscurshim I, Sabbagh C, Lynn PB, *et al.* Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: Impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys* 2014;88:822–8.

42. Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85:74–80.

43. Burbach JPM, Den Harder AM, Intven M, Van Vulpen M, Verkooijen HM, Reerink O. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: A systematic review and meta-analysis. *Radiother Oncol* 2014;113:1–9.

44. Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, Coquard R, *et al.* Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: The Lyon R96-02 randomized trial. *J Clin Oncol* 2004;22:2404–9.

45. Jakobsen A, Ploen J, Vuong T, Appelt A, Lindebjerg J, Rafaelsen SR. Dose-effect relationship in chemoradiotherapy for locally advanced rectal cancer: A randomized trial comparing two radiation doses. *Int J Radiat Oncol Biol Phys* 2012;84:949–54.

46. Rijkmans EC, Cats A, Nout RA, van den Bongard DHJG, Ketelaars M, Buijsen J, *et al.* Endorectal Brachytherapy Boost After External Beam Radiation Therapy in Elderly or Medically Inoperable Patients With Rectal Cancer: Primary Outcomes of the Phase 1 HERBERT Study. *Int J Radiat Oncol Biol Phys* 2017;98:908–17.

47. Rombouts AJM, Al-Najami I, Abbott NL, Appelt A, Baatrup G, Bach S, *et al.* Can we Save the rectum by watchful waiting or TransAnal microsurgery following (chemo) Radiotherapy versus Total mesorectal excision for early REctal Cancer (STAR-TREC study)?: protocol for a multicentre, randomised feasibility study. *BMJ Open* 2017;7:e019474.

48. Roels S, Duthoy W, Haustermans K, Penninckx F, Vandecaveye V, Boterberg T, *et al.* Definition and delineation of the clinical target volume for rectal cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1129–42.

49. Van Herk M, Remeijer P, Rasch C, Lebesque J V. The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:1121–35.

50. Urbano MTG, Henrys AJ, Adams EJ, Norman AR, Bedford JL, Harrington KJ, *et al.* Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. *Int J Radiat Oncol Biol Phys* 2006;65:907–16.

51. Mok H, Crane CH, Palmer MB, Briere TM, Beddar S, Delclos ME, *et al.* Intensity modulated radiation therapy (IMRT): Differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. *Radiat Oncol* 2011;6:63.

52. El-Gayed AAH, Bel A, Vijlbrief R, Bartelink H, Lebesque J V. Time trend of patient setup deviations during pelvic irradiation using electronic portal imaging. *Radiother Oncol* 1993;26:162–71.

53. Tan J, Lim Joon D, Fitt G, Wada M, Lim Joon M, Mercuri A, *et al.* The utility of multimodality imaging with CT and MRI in defining rectal tumour volumes for radiotherapy treatment planning: A pilot study. *J Med Imaging Radiat Oncol* 2010;54:562–8.

54. Jin P, van der Horst A, de Jong R, van Hooft JE, Kamphuis M, van Wieringen N, *et al.* Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer. *Radiother Oncol* 2015;117:412–8.

55. Beltran C, Herman MG, Davis BJ. Planning Target Margin Calculations for Prostate Radiotherapy Based on Intrafraction and Interfraction Motion Using Four Localization Methods. *Int J Radiat Oncol Biol Phys* 2008;70:289–95.

56. Oelfke U. Magnetic Resonance Imaging-guided Radiation Therapy: Technological Innovation Provides a New Vision of Radiation Oncology Practice. *Clin Oncol* 2015;27:495–7.

57. Brierley JD, Dawson LA, Sampson E, Bayley A, Scott S, Moseley JL, *et al.* Rectal motion in patients receiving preoperative radiotherapy for carcinoma of the rectum. *Int J Radiat Oncol Biol Phys* 2011;80:97–102.

58. Kleijnen J-PJE, van Asselen B, Burbach JPM, Intven M, Philippens MEP, Reerink O, *et al.* Evolution of motion uncertainty in rectal cancer: implications for adaptive radiotherapy. *Phys Med Biol* 2016;61:1–11.

59. Kleijnen J-PJE, van Asselen B, Van den Begin R, Intven M, Burbach JPM, Reerink O, *et al.* MRI-based tumor inter-fraction motion statistics for rectal cancer boost radiotherapy. *Acta Oncol (Madr)* 2019;58:232–6.

60. Vestermark LW, Jacobsen A, Qvortrup C, Hansen F, Bisgaard C, Baatrup G, *et al.* Long-term results of a phase II trial of high-dose radiotherapy (60 Gy) and UFT/l-leucovorin in patients with non-resectable locally advanced rectal cancer (LARC). *Acta Oncol (Madr)* 2008;47:428–33.

61. Seierstad T, Hole KH, Sælen E, Ree AH, Flatmark K, Malinen E. MR-guided simultaneous integrated boost in preoperative radiotherapy of locally advanced rectal cancer following neoadjuvant chemotherapy. *Radiother Oncol* 2009;93:279–84.

62. Mohiuddin M, Paulus R, Mitchell E, Hanna N, Yuen A, Nichols R, *et al.* Neoadjuvant chemoradiation for distal rectal cancer: 5-year updated results of a randomized phase 2 study of neoadjuvant combined modality chemoradiation for distal rectal cancer. *Int J Radiat Oncol Biol Phys* 2013;86:523–8.

63. Engineer R, Mohandas KM, Shukla PJ, Shrikhande S V., Mahantshetty U, Chopra S, *et al.* Escalated radiation dose alone vs. concurrent chemoradiation for locally advanced and unresectable rectal cancers: Results from phase II randomized study. *Int J Colorectal Dis* 2013;28:959–66.

64. Burbach JM, Verkooijen HM, Intven M, Kleijnen J-PPJEJ, Bosman ME, Raaymakers BW, *et al.* RandomizEd controlled trial for pre-operAtive dose-escaLation BOOST in locally advanced rectal cancer (RECTAL BOOST study): study protocol for a randomized controlled trial. *Trials* 2015;16:58.

65. Vorwerk H, Liersch T, Rothe H, Ghadimi M, Christiansen H, Hess CF, *et al.* Gold markers for tumor localization and target volume delineation in radiotherapy for rectal cancer. *Strahlentherapie Und Onkol* 2009;185:127–33.

66. Moningi S, Walker AJ, Malayeri AA, Rosati LM, Gearhart SL, Efron JE, *et al.* Analysis of fiducials implanted during EUS for patients with localized rectal cancer receiving high-dose rate endorectal brachytherapy. *Gastrointest Endosc* 2015;81:765–9.

67. Chan MF, Cohen GN, Deasy JO. Qualitative Evaluation of Fiducial Markers for Radiotherapy Imaging. *Technol Cancer Res Treat* 2015;14:298–304.

68. Gurney-Champion OJ, Lens E, Van Der Horst A, Houweling AC, Klaassen R, Van Hooft JE, *et al.* Visibility and artifacts of gold fiducial markers used for image guided radiation therapy of pancreatic cancer on MRI. *Med Phys* 2015;42:2638–47.

69. Vuong T, Devic S, Moftah B, Evans M, Podgorsak EB. High-dose-rate endorectal brachytherapy in the treatment of locally advanced rectal carcinoma: Technical aspects. *Brachytherapy* 2005;4:230–5.

70. Smith JA, Wild AT, Singhi A, Raman SP, Qiu H, Kumar R, *et al.* Clinicopathologic comparison of high-dose-rate endorectal brachytherapy versus conventional chemoradiotherapy in the neoadjuvant setting for resectable stages II and III low rectal cancer. *Int J Surg Oncol* 2012;2012:406568.

71. Corner C, Bryant L, Chapman C, Glynne-Jones R, Hoskin PJ. High-dose-rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. *Brachytherapy* 2010;9:66–70.

72. Chuong MD, Fernandez DC, Shridhar R, Hoffe SE, Saini A, Hunt D, *et al.* High-dose-rate endorectal brachytherapy for locally advanced rectal cancer in previously irradiated patients. *Brachytherapy* 2013;12:457–62.

73. Devic S, Vuong T, Moftah B, Evans M, Podgorsak EB, Poon E, *et al.* Image-guided high dose rate endorectal brachytherapy. *Med Phys* 2007;34:4451–8.

74. Vuong T, Devic S. High-dose-rate pre-operative endorectal brachytherapy for patients with rectal cancer. *J Contemp Brachytherapy* 2015;7:181–6.

75. Nout RA, Bekerat H, Devic S, Vuong T. Is Daily CT-Based Adaptive Endorectal Brachytherapy of Benefit Compared to Using a Single Treatment Plan for Preoperative Treatment of Locally Advanced Rectal Cancer? *Brachytherapy* 2016;15:S83–4.

76. Khoo VS, Joon DL. New developments in MRI for target volume delineation in radiotherapy. *Br J Radiol* 2006;79.

77. Swellengrebel HAM. Evaluating long-term attachment of two different endoclips in the human gastrointestinal tract. *World J Gastrointest Endosc* 2010;2:344.

78. Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, *et al.* Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy - 3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiolo. *Radiother Oncol* 2006;78:67–77.