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Planning study to compare two different strategies of rectal boost irradiation at the 1.5 T MR-Linac

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LIST OF ABBREVIATIONS

AJCC	American joint committee on cancer
APR	Abdominoperineal resection
ASR	Age-standardized incidence rates
ATP	Adapt-to-position
ATS	Adapt-to-shape
BMI	Body Mass Index
CB-CT	Cone-beam computed tomography
CRC	Colorectal cancer
cCR	Complete clinical response
CRM	Circumferential resection margins
CRT	Chemoradiotherapy
CT	Computed tomography
DFS	Disease-free survival
DICOM	Digital imaging and communications in medicine
Dmean	Mean dose
DRE	Digital rectal examination
DVH	Dose-volume histogram
DWI	Diffusion-weighted images
EMVI	Extramural vascular invasion
ERE	Electron return effect
ERUS	Endoscopic rectal ultrasound
ESMO	European society of medical oncology
FAP	Familial adenomatous polyposis
GTV	Gross tumor volume
HDI	Human development index
HU	Hounsfield units
IGRT	Image-guided radiotherapy
IQR	Interquartile range
IMRT	Intensity-modulated radiotherapy

LAR	Low anterior resection
LARC	Locally advanced rectal cancer
MR	Magnetic resonance
MRD	Magnetic resonance defecography
MRF	Mesorectal fascia
MRgRT	MR-guided radiotherapy
OAR(s)	Organ(s) at risk
OS	Overall survival
pCR	Pathological complete response
PET	Positron emission tomography
PROMs	Patient reported outcome measures
PTV	Planning target volume
QoL	Quality of life
QUANTEC	Quantitative analyses of normal tissue effects in the clinic
SIB	Simultaneous integrated boost
SPSS	Statistical package for social sciences
T	Tesla
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision
TNT	Total neoadjuvant therapy
TPS	Treatment planning system
TRG	Tumor response grade
UICC	Union for International Cancer Control
VMAT	Volumetric modulated arc therapy
W&W	Watch-and-Wait

1. INTRODUCTION

1.1. Overview

Rectal cancer is the second most common malignancy of the large intestine. An increasing number of new cases per year is diagnosed because of modern screening tools and access to them. When still localized in the pelvis, the 5-year relative survival rates for rectal cancer range from 72 to 89% [1, 2]. Local recurrence rates after curative treatment have decreased in time, from 10-30% in the past to 4-10% nowadays. Nevertheless, it remains a major clinical problem, since it presents with severe local symptoms, e.g., pain, bleeding, that influence negatively patient´s quality of life [3, 4]. Rectal cancer treatment is mainly based on the extent of the disease. The main therapeutic approaches include surgery, radiotherapy, and chemotherapy or a combination of them. In patients with locally advanced rectal cancer (LARC) and treated with pre-operative long-course chemo-radiotherapy (CRT), local recurrence rates range from 3.7% to 50%. Local recurrences carry a poor prognosis. The pathological response to the pre-operative treatment is an important prognostic factor for both local and distant control as well as for overall survival. However, on average in only 15% of the patients a complete response (pCR), defined as absence of cancer cells in the resected specimen, is achieved. Evidence suggests that radiotherapy (RT) dose escalation to the primary tumor may be a viable strategy to increase the pCR rate. Nevertheless, this is related with increasing risks of toxicity and therefore relies on reducing the irradiated volumes and identifying the optimal timing within the treatment schedule.

1.2. Anatomy and physiology

The rectum is located in the pelvis and is a segment of the large gastrointestinal tract. The rectum begins as a continuation of the sigmoid colon at the level of the sacral promontory and connects to the anus. The beginning of this part of the gastrointestinal tract can be marked by noting where the adventitial taeniae bands

have coalesced to form outer longitudinal muscle. At the junction of the rectum and the anal canal, there is a muscular ring – known as the anorectal ring. It is formed by the fusion of the internal anal sphincter, external anal sphincter and puborectalis muscle. The dentate line demarks the end of the rectum, namely the transition of columnar glandular epithelium of the large bowel to the squamous epithelium of the anal canal. The border between the colon and rectum has been defined differently and different measurement techniques are used. According to the European Society for Medical Oncology (ESMO), tumors with distal extension to ≤ 15 cm from the anal margin, defined by the dentate line, measured with rigid sigmoidoscopy are classified as rectal. Depending on the distance from the anal verge, rectal tumors can be subdivided in low (0–5cm), middle (>5cm–10cm) or high (>10cm–15cm) [5]. The superior third of the rectum is covered by peritoneum on its anterior and lateral surfaces. The middle third only has an anterior peritoneum covering and the lower 1/3 has no peritoneum associated with it, since it is located below the level of the peritoneal reflexion.

The entire length of the rectum is covered with perirectal fat, called mesorectum, containing the vessels for arterial supply, venous and lymphatic drainage together with lymph nodes. The mesorectal fascia (MRF) is a layer of connective tissue enclosing the perirectal fat that surrounds the rectum. The superior rectal artery, the continuation of the inferior mesenteric artery, is the principal artery supplying the rectum. Supplementary arteries which contribute to the blood supply of the rectum are the following: the middle rectal arteries, branches of the internal iliac arteries, with highly reported differences in frequency, they may be absent on one or both sides; the inferior rectal arteries, branches of the internal pudendal artery, the principal arteries supplying the anal canal; the median sacral artery, branch of the aorta, it arises just proximal to the aortic bifurcation and runs down the anterior aspect of the sacrum to terminate in the rectal wall.

The rectum has two drainage veins. The upper and middle thirds of the rectum drain primarily into the superior rectal vein and finally empty into the liver via the inferior mesenteric vein and portal vein. The lower third of the rectum drains into

the middle rectal vein, which drains directly into the inferior vena cava. Regarding the lymphatic drainage, the principal lymph nodes that receive most of the lymph from the upper two-thirds of the rectum are the inferior mesenteric lymph nodes which are situated around the origin of the inferior mesenteric artery. Lymph from the lower third of the rectum drains into three sets of principal nodes: the inferior mesenteric lymph nodes and the internal iliac lymph nodes bilaterally. Nerves from the first 3 lumbar segments of the spinal cord are responsible of the sympathetic innervation of the rectum and anal canal, while nerves from the caudal 3 sacral nerve roots (nervi erigentes) are responsible of the parasympathetic innervation. Together, sympathetic, and parasympathetic nerves form the pelvis plexus, which feeds the urinary and genital organs and the rectum. The anal continence is a very complex mechanism, which continues to be investigated. The rectum acts as a reservoir where the stool accumulates. The propulsion of the fecal mass from the large colon downward into the rectum is due to the peristaltic waves of the left colon. Once the rectum is distended, the internal sphincter relaxes while the external continues to keep continence. A complex iteration between environmental factors and reflexes of the anorectum results in inhibiting signals to the external anal sphincter and therefore its relaxation, which allows the fecal bolus to pass. Many techniques were developed to assess in patients eventual pelvic floor disorders such as manometry, dynamic MR imaging (dynamic magnetic resonance defecography MRD) [6] and endoanal ultrasound.

1.3. Incidence and epidemiology

Colorectal cancer (CRC) is the third leading cause of cancer death in the world, in both males and females, and the third most incident cancer, comprising 10% of all cancer diagnoses according to GLOBOCAN 2020 data [7-9]. In Germany about one in eight cancer diagnoses affects the colon or the rectum. In the 2020, 19 093 new cases of rectal cancer were diagnosed and the number of deaths from this disease was 8 892. Colorectal cancer incidence and mortality rates are strongly associated with the human development index (HDI). Arnold et al. [10]

analyzed the incidence and mortality pattern of CRC worldwide, based on GLOBOCAN database, and identified three different epidemiologic patterns correlated with the HDI:

1. increase in both incident and mortality in countries with medium HDI
2. increase of incidence but reduction in mortality in countries with high HDI
3. decline in both incidence and mortality in countries with the highest HDI as Japan, Australia, and New Zealand.

The introduction of screening programs, the changes in lifestyle and the implementation of the therapies may have led to a reduction of mortality.
There is growing evidence that risk factors associated with rectal cancer are distinct from those associated to colon cancer [11]. The identified risk factors for rectal cancer were:

- lack of exercise
- diet rich in red, processed, or charred meats
- high weight and high Body Mass Index (BMI)
- moderate/heavy tobacco and alcohol consume
- inflammatory bowel diseases (ulcerative colitis, Crohn´s disease)

Between 2% and 5% of CRC arise in the setting of hereditary syndromes, like the Lynch syndrome and the familial adenomatous polyposis (FAP).

1.4. Clinical presentation

Depending on tumor location and pattern of growth, clinical manifestations of rectal cancer may differ. Initial symptoms of localized rectal cancer may include incomplete evacuation, tenesmus, pain, iron deficiency anemia and change in bowel habits. Abdominal discomfort, fatigue and weight loss may be general, adjacent symptoms. In a retrospective analysis, among 2 750 patients with rectal cancer around 12% had emergency presentation. Along with the stage of disease, the need at the diagnosis of emergency interventions has a poorer outcome [12]. Since CRC usually causes symptoms in more advanced stages,

the implementation of screening programs has resulted in a larger proportion of patients with earlier-staged tumors and less symptoms.

1.5. Diagnosis and staging

The basis for the diagnosis of rectal cancer are the digital rectal examination (DRE) and the endoscopy with biopsy for histopathological examination. The distance of the primary tumor to the anal verge, as measured with rigid sigmoidoscopy, allows to classification of rectal cancer in low (≤ 5 cm), middle (> 5 cm and ≤ 10 cm) and high (> 10 cm) and based on which further decisions regarding treatment are made. A completion colonoscopy is also recommended to exclude synchronous colon tumors. The endoscopic rectal ultrasound (ERUS) can be used in early-stage tumors to assess the extent of invasion in the mucosa and submucosa but has limited value in locally advanced lesions.

In case of histologically confirmed invasive adenocarcinoma, a computed tomography (CT) scan of the thorax and abdomen is indicated to detect metastatic disease. Pelvic magnetic resonance imaging (MRI) is the preferred and the most accurate imaging modality for local staging of rectal cancer. By determining the involvement of the MRF, the extramural vascular invasion (EMVI) and the distance to the circumferential resection margins (CRM), the pelvic MRI can identify prognostic factors and, in the preoperative management, can define the extent of surgery. In contrast to other tumor sites, the use of the positron emission tomography (PET) for the preoperative staging is not routinely indicated. A PET scan should be performed to evaluated and better characterize equivocal findings detected with the CT scan or in patients with a strong contraindication to the intravenous contrast enhancement. Further diagnostic imaging as brain CT/MRT and bone scan should be performed only in case of symptoms warrant. Physical examination, complete blood count including liver and renal function and a geriatric assessment in elderly patients complete the diagnostic process and direct the best therapeutic path.

The staging of rectal cancer is done by the TNM classification system (Table 1). According to the current 8th edition isolated up to 20 tumor cells in the lymph

nodes are designated as N0 and clusters of 20 or more tumor cells i.e., micro-metastasis, as N1.

Table 1 UICC TNM-classification of colorectal cancer, 8th edition

T – Primary tumor	
Tx	*Primary tumor cannot be assessed*
T0	*No evidence of primary tumor*
Tis	*Carcinoma in situ**
T1	*Tumor invades the submucosa*
T2	*Tumor invades muscularis propria*
T3	*Tumor invades subserosa or into non-peritonealised pericolic or perirectal tissues*
T4	*Tumor directly invades other organs or structures, and/or perforates visceral peritoneum*
T4a	*Tumor perforates visceral peritoneum*
T4b	*Tumor directly invades other organs or structures*
N – Regional lymph nodes	
Nx	*Regional lymph nodes cannot be assessed*
N0	*No regional lymph node metastasis*
N1	*Metastasis in 1–3 regional lymph nodes*
N1a	*Metastasis in 1 regional lymph node*
N1b	*Metastasis in 2–3 regional lymph nodes*
N1c	*Tumor deposit(s), i.e., satellites, in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastasis*
N2	*Metastasis in 4 or more regional lymph nodes*
N2a	*Metastasis in 4–6 regional lymph nodes*
N2b	*Metastasis in 7 or more regional lymph nodes*
M – Distant metastasis	
M0	*No distant metastasis*
M1	*Distant metastasis*
M1a	*Metastasis confined to one organ without peritoneal metastases*
M1b	*Metastasis in more than one organ*
M1c	*Metastasis to the peritoneum with or without other organ involvement*

*Invasion of the lamina propria, but without extension through the muscularis mucosae

Table 2 Stage grouping of colorectal cancer

Stage	**T**	**N**	**M**
Stage 0	Tis	N0	M0
Stage I	T1-T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1	M0
	T1	N2a	
Stage IIIB	T1-T2	N2b	M0
	T2-T3	*N2a*	
	T3-T4a	N1	
Stage IIIC	T3-T4a	N2b	M0
	T4a	N2a	
	T4b	N1-N2	
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

1.6. Postoperative staging (pathological assessment of response)

After neoadjuvant CRT the tumor regression rate must be assessed to estimate the prognosis and the effects of therapy. Many are the tumor regression grade (TRG) systems used in clinical practice. The TRG systems according to Mandar [13], Dworak [14], Becker [15] and Rödel [16] are the most common used. These principal systems are summarized in Table 3.

Table 3 Overview of the principal tumor regression grade (TRG) system

	Mandar	Dworak	Becker	Rödel
No Regression	Absence of regressive change (TRG 5)	No regression (TRG 0)	> 50% residual tumor/tumor bed (Grade 3)	No regression (TRG 0)
	Residual cancer outgrowing fibrosis (TRG 4)	Dominant tumor mass with obvious fibrosis and/or vasculopathy (TRG 1)	10-50% residual tumor/tumor bed (Grade 2)	Regression of <25% of the tumor mass (TRG 1)
	Fibrosis outgrowing residual cancer (TRG 3)	Dominantly fibrotic changes with few tumor cells or groups (TRG 2)		Regression of 25-50% of the tumor mass (TRG 2)
	Rare residual cancer cells (TRG 2)	Very few tumor cells in fibrotic tissue with or without mucous substance (TRG 3)	< 10% residual tumor/tumor bed (Grade 1b)	Regression of >50% of the tumor mass (TRG 3)
Complete regression	No residual cancer (TRG 1)	No tumor cells, only fibrosis (TRG 4)	No residual tumor/tumor bed (Grade 1a)	Complete regression (TRG 4)

There is no consensus on the optimal scoring system. The ESMO guidelines suggest that as a minimal required information in the pathological report, it must be reported if the tumor had either complete response, partial response, or no

response. The extramural venous invasion (EMVI), defined as invasion of veins beyond the muscularis propria by tumor cells, is another histopathological feature that can define the outcome. Chand et al [17] analyzed the influence of the EMVI on the DFS rate in patients with stage II and II rectal cancer. The authors reported that the EMVI is an independent prognostic factor of poor outcome (HR 2.08; 95% CI 1.10-2.95) and that in case of EMVI-positivity the risk of disease recurrence was independent from tumor stage.

1.7. Treatment

The multidisciplinary team conference (MDT) includes different specialists involved in the care of patients with rectal cancer, i.e., surgeons, radiologists, medical oncologists, radiation oncologists, pathologists, and specialized nurses. The role of the MDT is to define the best diagnostic and therapeutic approach for each patient, based on risk assessment and stage.

The treatment options for rectal cancer include surgery, chemotherapy, target therapy, radiotherapy, and active surveillance are as follows discussed in detail.

1.7.1. Surgery

For the treatment of primary rectal lesions, a variety of surgical approaches, including minimal invasive techniques and more invasive procedures are employed.

In early stage, low grade rectal cancer without adverse features as vascular- and lymphatic invasion (L1, V1) local excision procedures, i.e., the transanal endoscopic microsurgery (TEM), introduced in 1983 [18] can be used as only therapeutic approach. This procedure consists in a full-thickness excision of rectal lesions perpendicularly through the rectum wall into the perirectal fat. To be defined as successful, deep and mucosal margins must be > 3 mm. In cTis-cT1N0 tumor stages a local excision can provide similar oncological results achieved with the total mesorectal excision (TME) with the advantage of preserving the anorectal function and reduce morbidity and rapid postoperative recovery [19].

When the requirements for a local surgery are not met, a transabdominal resection should be performed. In 1982 the concept of TME was introduced by Professor R.J Heald and consists in the complete removal of the rectum, including the surrounding mesorectum through a sharp dissection along the visceral fascia, that Professor Heald defined “Holy plane”. This technique was designed with the aim to minimize residual tumor, by removing the complete vascular and lymphatic structures, while sparing the autonomic nerves [20]. Depending on the tumor localization and its extension, different surgical procedures combined with TME can be performed. The low anterior resection (LAR) is the preferred technique in patients with high or mid rectal cancer. The LAR consists in a TME extended to 5 cm below the distal edge of the primary lesion, followed by the creation of a colorectal anastomosis, allowing patients to avoid the permanent colostomy. With an abdominoperineal resection (APR) rectosigmoid, anal sphincter and perianal soft tissue are completely removed. This procedure requires a creation of a colostomy [21] and is performed in case of infiltration by the tumor of the anal canal or the levator muscles. Over the years, there has been a progressive reduction in the number of APR performed. Schoetz et al analyzed the evolution of the practice patterns in the colorectal surgery over a 12-year-period, from 1994 to 2005. In this analysis the LAR outnumbered APR by a 3-to-1 ratio [22]. Despite these data, the APR has not completely disappeared from the surgical records.

Interval to surgery after preoperative CRT

The optimal time to surgery after preoperative CRT is still debated. The reasons for this “planned” delay are to allow patients to recover from the acute reactions of the CRT and thus to perform a safer surgery and to reach a maximal effect of the radiotherapy, but at the same time avoiding tumor repopulation. When a short-course preoperative radiotherapy (25 Gy as total dose at 5 Gy/fraction during one week; see chapter 1.7.3) is performed, an immediate surgery within 10 days from the start of the radiation treatment is recommended. In a prospective, randomized, multicenter trial conducted by Evans et al [23] tumor

downstaging (T Stage) and rate of pCR after 6 and 12 weeks from the end of CRT were compared. A significant larger proportion of downstaging in the 12-weeks group compared to the 6-weeks group was found (58% vs 43%, respectively), as well as a higher rate of pCR (20% vs 9%, respectively). In contrast, the GRECCAR-6 trial, in which time intervals to surgery of 7 and 11 weeks were compared, reported no statistically significant difference in the pCR rate (15% vs 17.4%, respectively) [24].

1.7.2. Chemotherapy

Neoadjuvant chemotherapy

The use of chemotherapy in combination with radiotherapy in a preoperative setting (neoadjuvant chemoradiotherapy) is recommended for newly diagnosed rectal cancers in stage II (cT3-T4, cN0) and stage III (node-positive disease), based on endoscopy and contrast-enhanced MRI. The agents commonly used are 5-Fluorouracil (5-FU), Capecitabine (an oral pro-drug of the 5-FU) and Oxaliplatin. 5-FU and Capecitabin are antimetabolites that prevent cell proliferation by inhibiting the enzyme thymidylate synthase and therefore blocking the thymidine formation required for DNA synthesis. At first Capecitabin was approved by the FDA in 2001 for the treatment of metastatic colorectal patients. Subsequently and based on the X-ACT trial [25], its use was extended to the adjuvant treatment of patients with colon cancer, as its noninferiority to the intravenous bolus of 5-FU was demonstrated. Oxaliplatin is made up of heavy metal compounds that inhibit synthesis of RNA, DNA, and protein in cells. Mostly, Oxaliplatin exerts its cytotoxic effect through DNA damage. When compared to radiotherapy alone, concurrent neoadjuvant chemoradiotherapy in patients with stage II-III rectal cancer improves local control, functioning as local sensitization to the radiotherapy. Locally recurrent rectal cancer after primary treatment is today still a clinical challenge, associated to poor quality of life and a limited survival time. The FFCD 9203 trial [26] demonstrated that adding 5-FU to preoperative radiotherapy reduces the 5-years incidence of local recurrence from 16.5% to 8.1% and increases the rate of pathological complete remissions from 3.6% to 11.4%. No difference in 5-year OS was reported.

Adjuvant chemotherapy

In colon cancer, an adjuvant 5-FU-based chemotherapy in stage II and III has an established role in increasing OS [27]. In rectal cancer, the benefit of an adjuvant systemic therapy is unclear. Some trials have shown an increase in DFS and OS when patients were treated only with surgery [28], though randomized trials and meta-analyses have not shown any benefit in the use of adjuvant 5-FU in patients underwent preoperatively to chemoradiotherapy [29, 30]. The current ESMO guidelines suggest that an adjuvant chemotherapy could be considered and risk-balanced in rectal cancer patients who underwent preoperative CRT with a pathological stage II or III.

1.7.3. Radiotherapy

Radiotherapy in the treatment of rectal cancer has three major aims:

- Increase of local control
- Downsizing the primary resectable tumor located in the middle-low rectum with the aim to perform sphincter-sparing surgery
- Downstaging the primary irresectable tumor.

Radiotherapy can be used in a neoadjuvant or adjuvant setting as well as primary treatment, in most of the cases combined with chemotherapy.

Neoadjuvant (chemo)radiotherapy

For patients with LARC (stage II and III), treatment decisions are made based on pre-operative MRI, which can identify prognostic factors of local recurrence [31]. With the aim to reduce the risk of local recurrence, neoadjuvant CRT can be performed in patients with resectable rectal cancer, in which negative prognostic factors of local relapse or synchronous metastatic disease in the preoperative MRI are identified. By predicting the possibility to achieve a complete mesorectal excision and clear CRM > 1mm, preoperative MRI plays a key role in the indication of a neoadjuvant treatment in resectable rectal cancer.

Another indication for neoadjuvant CRT is for unresectable locally advanced rectal cancer. Using the MRI, rectal cancers that are unlikely to be amenable to

a curative excision are defined as unresectable. However, there is no precise definition of “unresectable”. In those circumstances, neoadjuvant CRT is necessary to shrink the primary tumor, so that it is confined at the time of surgery in the threatened margins, i.e., the MRF. Chemotherapy in addition to the radiotherapy serve as radiosensitizer to enhance the effect of radiotherapy. In a phase III, randomized trial conducted by Brændengen et al, RT alone was compared to CRT (fluorouracil/leucovorin) in patients with unresectable cT4 rectal cancer. The authors found an improvement in both 5-years local control and overall survival in the group treated with CRT (82% vs 67% and 66% vs 53%, respectively) [32].

Fractionation

Nowadays, two RT regimes are commonly used in the neoadjuvant setting and defined as standard of care: long-course (chemo)radiotherapy and short-course radiotherapy. In the long course, conventionally fractionated schedule doses of 50-50.4 Gy in 25-28 fractions (1.8-2 Gy per fraction, 5 fractions per week) are given with concomitant chemotherapy (5-FU or Capecitabine). In the short course radiotherapy 25 Gy are given in 5 fractions (5 Gy per fraction, 5 fraction per week), followed by immediate or delayed surgery. In the Stockholm III trial short-course radiotherapy followed by immediate surgery within 1 week and the same regime with surgery delayed for 4–8 weeks were compared and no difference in local recurrence rate and in oval survival were found [33].

This schedule was first introduced in 1977 in Uppsala, due to discussions between surgeons and oncologist about the management of locally relapsed rectal patients: with the aim of being able to treat those patients during the hospitalization for the surgical resection, a schedule of 25.5 Gy in 5 fractions was proposed. Thereby, patients with locally relapsed disease were treated with preoperative radiotherapy during one week of hospitalization with surgery planned for the week after.

Later, this schedule was used in a phase II trial where only 5% of local failures were seen after a follow up of two years [34]. So far, there is no clear definition in which tumor stages the long-course or the short-course RT should be preferred.

In two randomized trials patients with T3-T4 resectable rectal cancer were randomized to receive either long-course RT or short-course RT. In both trials no difference in terms of local control, DFS and OS was found between the two RT schedules [35, 36]. In the RAPIDO trial, patients with high-risk LARC (with at least one of the following criteria detected with the MRI: stage cT4a or cT4b, cN2, extramural invasion, involved MRF, or enlarged lateral lymph nodes) were treated with short-course RT followed by chemotherapy and TME and compared with standard CRT. The authors found a significant reduction in the cumulative probability of distant metastases in the shot-course group compared with the standard of care group (at 3 years, 20% vs 26.8%, respectively). Moreover, in the experimental group the pCR rate was double that of the standard of care group (28% vs 14%, respectively) and no differences in locoregional control and overall survival after 3 years was described [37].

Adjuvant radiotherapy

For long time, adjuvant CRT was the standard of care for the treatment of LARC (stage II and III) [38, 39]. Later, data that showed the superiority of the preoperative CRT in terms of local control and toxicity and that led it to become the new standard of care in locally advanced disease were published [40]. When surgery is performed as primary treatment, the adjuvant radiotherapy could be used in patients, in which unexpected adverse histopathological features, as perforations in the tumor area, positive CRM, positive lymph nodes with extracapsular spread, are found and therefore when the risk of local relapse is high [5].

1.7.4. ‘Watch-and-wait’

Following neoadjuvant CRT, the response assessment is performed usually after 12 weeks with DRE, endoscopy, MRI, and biopsy. The clinical complete response (cCR) is defined as absence of any palpable or visible induration or irregularity at the digital examination, absence of residual tumor or suspect lymph nodes at the MRI and negative biopsies from the location of the primary rectal lesion. The rate

of cCR after neoadjuvant CRT reported in literature varies from 10% to 40%, depending on the initial stage of disease.

There is increasing evidence that, in patients treated with neoadjuvant CRT, surgery can be deferred when a cCR is achieved. Dr. Habr-Gama and her group of the University of São Paulo School of Medicine (Brazil), pioneers of the watch-and-wait (W&W) strategy, published the first encouraging data about the excellent local control and overall survival in patients managed with a non-surgical approach [41, 42]. In a more recent meta-analysis conducted by Dossa et al, 23 studies (867 patients) were included and no significant differences in non-regrowth recurrence, defined as non-luminal intrapelvic relapse or distant metastases, or overall survival in patients treated with non-surgical and surgical approach was observed [43].

The main advantage of the W&W strategy is to avoid morbidity and mortality risks associated with the surgery and to increase quality of life. Moreover, salvage surgery can be used as radical treatment in case of local recurrence. This implies that such patients most undergo to rigorous and more frequent surveillance to allow a feasible and timely salvage surgery.

1.8. Aims and objectives

The new MR-Linac system allows online-adaptive treatments based on daily high-quality MR images for the re-definition of target volumes and organs at risk (OARs) in combination with daily online re-optimization of the treatment plans. This implies that position, form, and volume changes of target volumes (tumor shrinkage) as well of OARs are detected and the daily plan is accordingly adapted while the patient lies on the treatment table (online adaptation). In addition, MR imaging while the treatment beam on allows intrafractional motion monitoring which secures high-precision delivery of the adapted plan.

To explore the potential opportunities of online MR-guided response-adaptive boost irradiation in patients with rectal cancer, this doctoral thesis focusses on three potential drawbacks of current cone-beam CT image-guided non-adaptive radiotherapy. First, at the conventional cone-beam CT-based linac the gross

tumor volume cannot be clearly detected. Therefore, dose escalation (boost) to the tumor without risk to the surrounding normal tissues limits the therapeutic window. Second, the variation from day to day in the tumor position requires large safety margins to avoid target miss which in turn further narrows the opportunities for additional radiation dose without excess side effects. Third, non-adaptive boost strategies miss the opportunity of smaller radiation volumes in case of tumour shrinkage throughout the course of fractionated radiotherapy. Such a shrinkage has been observed in a prospective study, where rectal tumor volume changes were monitored using weekly MRI with an average reduction of 54% during CRT was found [44].

Therefore, the hypothesis of the present planning study was that an adaptive-MR guided boost with small margins sufficient to cover intrafraction motion uncertainty will be dosimetrically superior to an up-front non-adaptive boost. The study was designed to compare two different, MRI-based rectal boost strategies: an up-front boost strategy irradiating as performed in a prior dose-escalation trial [45]. The boost was delivered in five consecutive days prior to the start of the course of fractionated radiotherapy over 5 weeks. In contrast, the adaptive boost is meant to be delivered once a week over the entire treatment course.

The treatment on the MR-Linac system is very time consuming with a mean treatment time of 20 min on every day. Therefore, intrafraction motion plays an important role and was quantified in the present study as the difference in position between the start and the end of the treatment session. This part of the study aims to establish a safety margin concept for future online MR-guided radiotherapy trials in rectal cancer. Based on the results of the planning study, a first-in-man application has been performed.

2. MATERIALS AND METHODS

The planning study and the evaluation of the first-in-man application were approved by the Ethics committee of the Medical Faculty Tübingen (444/2021A and 659/2017BO1). Parts of the results were published in full text publications listed in chapter 9 of the present thesis [46, 47].

2.1. Planning study

Patients and treatment characteristics

For the planning study data from patients treated at the MR-Linac with histologically confirmed locally advanced adenocarcinoma of the middle- or low-rectum (stage II-III) were used. The following inclusion criteria were applied: clinical stage II or III with an indication for neoadjuvant, long-course CRT. Exclusion criteria were any clinical conditions precluding the standard treatment with radiochemotherapy and any contraindications to MRI, such as claustrophobia or electronic devices including defibrillators, cochlear implants or pacemakers. Before start of treatment, patients were staged with clinical examination, blood test for bone marrow, renal and hepatic function, endoscopy with biopsy, contrast-enhanced thorax and abdomen computed tomography CT to exclude metastatic lesions and a gadolinium-enhanced pelvic MRI.

For radiotherapy planning a CT (Brilliance Big Bore, Philips, Eindhoven, The Netherlands) and MR simulation (Elekta Unity®, Elekta AB, Stockholm, Sweden) were performed on the same day with manually corrected rigid automatic registration to align the planning CT with the MR.

As part of the standard procedure in our department, patients were instructed to drink approximately 400 cc of water and to empty the bowel before the simulation scans were taken. The simultaneous chemotherapy consisted of a continuous intravenous infusion of 5-FU at a dose of 1000 mg/m2 per day over 5 days during the first and the last week of treatment. A radiation dose of 50.4 Gy in 28 fractions was prescribed and a 7 MV photons step-and-shoot IMRT plan for the 1.5 T MR-Linac was generated using the treatment planning system (TPS) Monaco® 5.4

(Elekta AB, Stockholm, Sweden). Eight weeks after the end of the treatment patients underwent a re-staging MRI and were planned for subsequent surgery with LAR or APR.

MR images acquisition

During each treatment fraction, T2-weighted scanning was performed before and after radiation delivery and the data sets were named pre-treatment T2w-2 min and post-treatment T2w-2min. The pre-treatment T2w-2min scans were used to adapt the reference plan applying virtual couch shifts and subsequent segment weight optimization (adapt-to-position ATP workflow) [32]. The post-treatment T2w-2min scans were acquired for quality assurance, research purposes and to evaluated patients' movement during irradiation. At the end of the first 5 fractions (after irradiation) and then once a week, the following additional MRI sequences were acquired: T2-weighted 3D pseudo steady-state (pss) (T2w-6min) and T2-weighted 3D fat suppression SPAIR (T2w-SPAIR). Table 4 summarizes the MR parameters used in the present investigation.

Table 4 Magnetic resonance imaging parameters

Parameter	**pre-/post-treatment T2-weighted (T2w-2min)**	**T2-weighted 3D pseudo steady state (T2w-6min)**	**T2-weighted 3D fat suppression (T2w-SPAIR)**
Matrix size	268 × 267	332 × 371	308 × 343
FOV (mm^3)	400 × 400 × 300	400 × 448 × 270	400 × 446 × 270
Voxel (mm^3)	1.5 × 1.5 × 2	1.2 × 1.2 × 1.2	1.3 × 1.3 × 1.3
TE (ms)	278	168	145
TR (ms)	1535	1300	1300
Flip angle (°)	90	90	90
WFS (pix) / BW (Hz)	0.293 / 740.3	0.519 / 418.3	0.541 / 401.8
Acquisition time (min)	1:57	6:01	6:09

FOV, field of view; TE, echo time; TR, repetition time; WFS, water-fat shift; BW, bandwidth

Boost strategies and target definition

To address the hypothesis of our planning study, we compared 4 different boost strategies according to boost-timing (Fig. 1) and PTV margins:

1. *Up-front boost with standard PTV margins*: a boost of 15 Gy to the gross tumor volume (GTV) in 5 daily fractions during the first week of treatment with an anisotropic PTV margin, 7 mm laterally and 10 mm in all other directions, followed by the standard treatment.
2. *Up-front boost with reduced PTV margins:* a boost of 15 Gy to the GTV in 5 daily fractions during the first week of treatment with an isotropic 3 mm PTV margin followed by the standard treatment.
3. *Adaptive boost with standard PTV margins*: a boost of 15 Gy to the GTV in 5 fractions with one boost fraction per week during the standard treatment and with an anisotropic PTV margin, 7 mm laterally and 10 mm in all other directions.
4. *Adaptive boost with reduced PTV margins:* a boost of 15 Gy to the GTV in 5 fractions with one boost fraction per week during the standard treatment and with an isotropic 3 mm PTV margin.

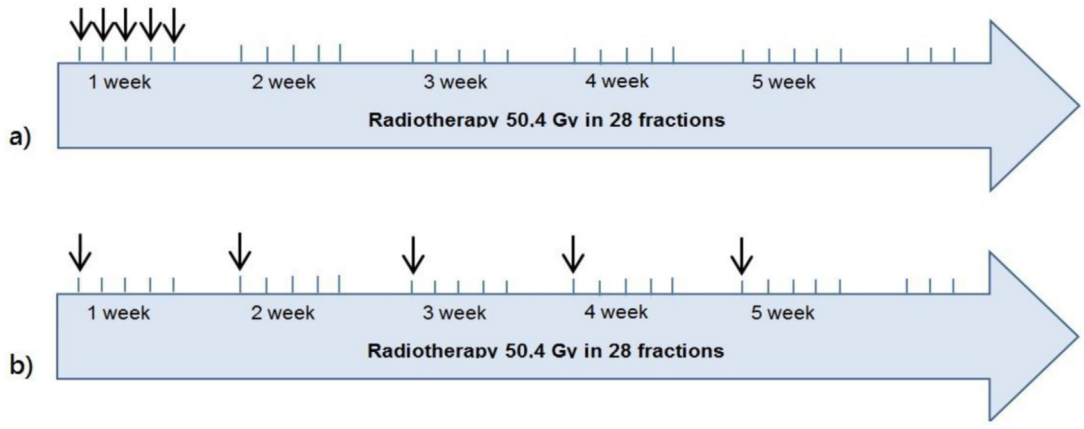

Figure.1 Study design with time points for imaging and boost planning for a) Up-Front and b) Adaptive boost

To calculate the biologically equivalent dose normalized to 2 Gy per fraction (EQD2) we used the linear-quadratic iso-effect model with an α/β value of 10 Gy for tumor and 3 Gy for the OARs:

$$EQD2 = D\ \frac{d+\alpha/\beta}{2+\alpha/\beta}$$

Adding the dose of the standard treatment (50.4 Gy in 28 fractions) to the boost dose, the total EQD2 to the primary tumor was 66.25 Gy.

For each patient, the OARs were defined in all T2w-6min images according to the Radiation Therapy Oncology Group contouring guidelines [48]. The anal sphincter was defined as the muscle layer around the anal canal. Other OARs and respective dose parameters include rectum (Dmean, V60, V65), bladder (Dmean, V40), anal canal (Dmean), and penile bulb (Dmean). To additionally inform the GTV definition, the T2w-SPAIR were registered to the respective T2w-6 min images.

Planning

For every patient a CT-based treatment plan with 50.4 Gy prescribed to the PTV was retrospectively optimized. In addition, a CT-based treatment plan was optimized on the MR-based adapted boost volume. For each patient, boost plans were based on the optimization criteria listed in Table 5. The iso-effects were adapted within the planning process to ensure adequate PTV coverage.

Every treatment plan was optimized within the treatment planning system (TPS) Monaco 5.4 (Elekta AB, Stockholm, Sweden) in a nine-beam step-and shoot technique with the fixed beam angles (180 °, 140 °, 95 °, 60 °, 20 °, 340 °, 300 °, 265 °, 220 °), a 3 mm dose grid and 1% calculation uncertainty. Further optimization parameters are shown in Table 6.

Table 5 Optimization criteria adopted for the boost plans

Prioritization	Structure	Prescription	Power Law Exponent	Isoconstraint	Reference Value	Shrink Margin
	PTV Boost	Target EUD	-	15,00	Cell Sens= 0,50	
		Quadratic Overdose	-	0,4	Max Dose= 15,00 Gy	
		Target Penalty	-	14,25	Min Vol = 96%	
2	Sigmoid	Serial	1	1,5		0,6 cm
		Quadratic Overdose	-	14	0,10	-
	patient	Quadratic Overdose	-	13	0,05	0,0 cm
4		Conformality	-	0,45	-	-
3	Bladder	Serial	8	4,9	-	-
	BowelBag	Serial	1	1	-	-
		Quadratic Overdose		0,1	Max Dose= 15,00 Gy	-
	Rectum	Quadratic Overdose		0,22	Max Dose= 15,00 Gy	-
1		Serial	1	11		-
	Vagina	Serial	3	2		-
	AnalCanal	Serial	14	2		-

Table 6 Plan optimization parameters

Optimization Criteria	Criterion
Delivery Mode	Step & Shoot
Max Number of Segments	250
Min Segment Area (cm^2)	2,5
Min MU / Segment	4,00
Min Segment Width	0,6 cm

Simulated dose distributions on the MRI of the day were planned based on the MR-Linac adapt-to-shape ATS workflow [49] using a synthetic CT with mean densities of the primary CT assigned to femur, pelvis, sacrum, rectum, bladder and not further defined soft tissue. Within the MR-based optimization for all treatment plans, the iso-effects on the OARs lowered following the constraint priority listed in Table 5. Therefore, in a first step the rectum serial constraint was tightened until the PTV coverage D98 = 14.25 Gy (95% of the prescribed Dose) ± 0.1 Gy. Once the best rectal sparing was achieved, an equivalent tightening of the sigmoid, bladder and conformality towards the PTV was done.

Intra-fractional motion assessment

To assess the intra-fractional motion, we propagated the GTVs contoured in the T2w-6 min images (post-treatment) in the pre-treatment T2w-2min. On these scans, the contours were edited and adapted to the pre-treatment anatomy. The open-source DICOM toolkit (DCMTK) was used to create masks of the GTV contours identifying voxels occupied by GTV in the pre and post treatment scan on a MRI voxel grid of 0.83 x 0.83 x 1 mm3. For every voxel of the post-treatment GTV, a minimal Euclidean distance to a voxel occupied by the GTV in the pre-treatment scan was calculated in Matlab (Version 2020). For this voxel-based minimal distance, the percentage GTV coverage for isotropic margins from zero to 20 mm was calculated.

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS, version 26, Inc., Chicago, IL). The nonparametric Wilcoxon signed-rank test was used to evaluate the differences between pairwise comparisons. A one-tailed p-value was calculated and p 0.05 was considered statistically significant.

2.2. Case report

Patient´s characteristics

A 73-year-old patient was diagnosed with a synchronous adenocarcinoma of the ascending colon and of the lower rectum. A colonoscopy performed in March 2021 showed a stenotic, circular mass in the ascending colon with a length of 5 cm. Moreover, the colonoscopy revealed also a non-stenotic lesion of the low rectum with distal edge 5 mm from the dentate line and a longitudinal extension of 4.5 cm. Pathological examination of both colon and rectal lesions revealed well-differentiated adenocarcinoma. A contrast-enhanced CT and a gadolinium contrast-enhanced pelvic MRI were performed, and distant metastases were excluded. Due to symptomatic bowel stenosis, the patient underwent emergency right hemicolectomy. The definitive pathology of the colon cancer revealed a pT4a pN0 cM0 stage. Clinically, the rectal cancer was staged as cT3a cN0. The case was discussed at the interdisciplinary tumor board of the CCC Tübingen-Stuttgart and two possible strategies were proposed for the treatment of the rectal cancer. As a standard approach radiochemotherapy followed by surgery, which would have required permanent colostomy or a low anastomosis with a high risk of suboptimal anorectal function. Since the patient underwent already a major surgery with removal of a large amount of colon, an alternative approach consisting in radiochemotherapy with radiation dose escalation and wait-and-see policy was proposed. After careful consultation and sufficient time for consideration the patient chooses the latter option.

Planning and treatment

The radiation treatment (base plan) consisted of 45 Gy given in 25 fractions with 5 fractions per week to the primary tumor, mesorectum and internal iliac lymph nodes. A simultaneous integrated boost (SIB) at the dose of 2 Gy per fraction was prescribed to the primary tumor volume. In addition, for radiation dose escalation an adapted MR-guided boost was prescribed to the primary tumor. The boost consisted of 3 Gy per fraction, scheduled once a week as the sixth fraction at least six hours after the previous fraction. This boost concept was adopted from the previously published RECTAL-BOOST phase II trial. In this

study, the boost intervention consisted of a sequential boost to the primary tumor of 15 Gy at 3 Gy per fraction given five consecutive days before the start of radio chemotherapy [45]. However, based on the results of our previous planning study we opted for a response-adapted weekly boost throughout the course of five weeks to exploit tumor shrinkage. Moreover, we decided to apply the boost after application of endorectal gel filling. It was already reported that the use of endorectal filling for diagnostic pelvic MRI improve the accuracy of localizing the rectal tumor [50]. Besides better visualization of the target, additional distancing of the adjacent healthy rectal mucosa during the boost irradiation was achieved by this maneuver. The patient underwent a CT simulation (Brilliance Big Bore, Philips, Eindhoven, The Netherlands) in supine position with full urinary bladder and empty rectum. At the same day, the MR simulation took place at the 1.5T MR-Linac (Elekta Unity®, Elekta AB, Stockholm, Sweden) and it was performed with and without 100 cc rectal ultrasound gel. Step-and-shoot IMRT treatment plans were prepared using Monaco 5.4 (Elekta AB, Stockholm, Sweden).

During the planning phase, a dedicate phantom was used to correlate gel density with the corresponding Hounsfield units (HU). For the ultrasound gel, a mean HU of 8 was found and, in the dose calculation process, considered water-equivalent; the same electron density as the surrounding tissue was assigned [51].

For the boost dose escalation, the GTV was defined based on the daily MRI and an isotropic expansion of 5 mm was made to generate the PTV and thus to account for intra-fractional motion. The OARs were defined according to the Radiation Therapy Oncology Group contouring guidelines [48]. To quantify the dosimetric benefit of our boost strategy the rectal wall was defined as the rectum imploded by 2 mm on the level of the boost PTV and an additional 1 cm longitudinal expansion.

All treatment fractions of the base plan and boost were performed on a 1.5 T MR-Linac. For the daily base plan (45/50 Gy in 25 fractions), the adapt-to-position ATP workflow was applied. In case of major anatomical variation on the given day (e.g., major changes in rectum air filling or bladder filling), an adapt-to-shape ATS workflow was applied. For all the boost fractions the ATS workflow was used.

Concomitant chemotherapy with 5-fluorouracil (1000 mg/m² per day) was given in the first and last week of treatment as continuous venous infusion over 5 days. To evaluate patient's health condition and to assess the tolerance to the treatment, patient reported outcome measures (PROMs) were weekly filled using the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) scale as well as a treatment experience questionnaire for the MR-guided radiotherapy.

Boost workflow

On every boost fraction, 100 cc of ultrasound gel were injected into the rectum. Then, the patient was positioned on the treatment table in the same position as in the CT and MRT simulation. A pre-treatment T2w-2min scan was acquired and fused with the reference CT scan. After this, the OARs including rectum and bladder were delineated by the physician and dose calculation was started to generate a new plan based on the anatomy of the day. After plan approval and secondary dose calculation, the daily radiation dose was applied while live cine imaging to monitor any possible intra-fraction changes of anatomy or GTV position was conducted [52]. After completion of radiation a post-treatment T2w-2min scan was acquired. Target volume coverage during beam-on was determined by post-hoc delineation of the primary tumor in the post-treatment T2w-2min scan.

Intra-fractional motion assessment with ultrasound gel filling

The hypothesis underlying this evaluation was that, with the use of the endorectal gel filling, in addition to a more accurate definition of the tumor volume, it may be possible to limit intra-fractional movements of the rectal lesion and thereby reduce PTV margins. For this purpose, the diagnostic MRI scans of ten rectal cancer patients routinely conducted with rectal ultrasound gel filling had been used to estimate the motion of the primary tumor. The primary tumor was segmented in the T2w scans and in the T1w contrast enhanced sequences, which have been acquired the one at least 20 minutes after the other. The annotated structure sets of each patient were processed in Matlab R2020a (Mathworks Inc., Natick, MA,

USA) for the calculation of a 1 × 1 × 1 mm³ binary voxel grid with a structure interpolation between discrete slice levels (Fig 2).

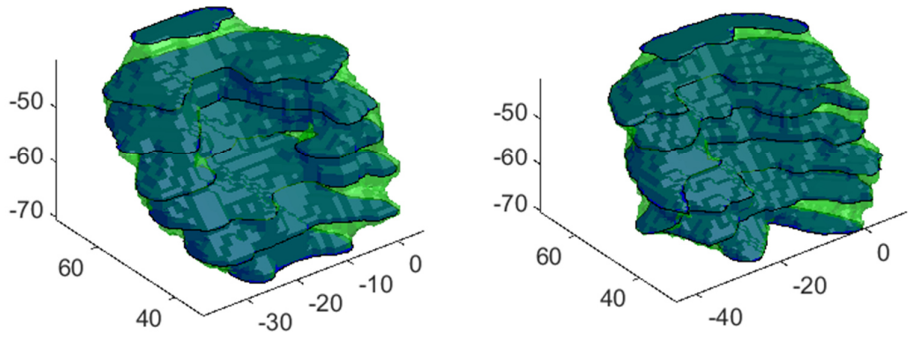

Figure 2 Exemplary visualization of the contour based on the pre-treatment T2w-2min MRI on the left and post-treatment T2w-2min MRI on the right. Blue depicts the contoured slices on the MRI and green the interpolated voxel grid.

For each patient, 95% Hausdorff distance between the two GTVs and GTV coverage of the second time point was determined for isotropic margins up to 20 mm as well as an average was calculated.

3. RESULTS

Parts of the results were published in full text publications listed in chapter 9 of the present thesis [46, 47].

3.1. Planning study

Patients and tumor characteristics

Five patients with histologically confirmed LARC were included in the analysis. The median age was 55 years (range 52-73). All patients had a rectal cancer in stage II or III of the middle- or low-rectum with a median distance of the primary tumor from the anal verge of 7 cm (range 2-9). At the beginning of the treatment, the primary tumor had a median volume of 19.4 cm^3 (range 7.5-52.5). All patients completed the neoadjuvant CRT with 50.4 Gy and 5-fluorouracil as prescribed without interruptions, unplanned breaks or radiation/chemo dose reductions. Table 7 summarizes patient and tumor characteristics of the patients enrolled in the present planning study.

Table 7 Patient and tumor characteristics

Patient	**Age** (years)	**Gender**	**Stage**	**Primary tumor size***		**Distance from anal verge** (cm)*
				Length (cm)	**Volume** (cm^3)	
1	54	female	T3N1M0	4	7.5	9
2	52	female	T2N1M0	2.8	22.6	7
3	65	male	T3N1M0	6	52.5	2
4	55	male	T3N1M0	3	10.4	6
5	73	female	T3N1M0	6.2	19.4	9

*The volume of the primary tumor as well as length and distance from the anal verge were measured on baseline diagnostic MRI (the distance from sphincter was measured on sagittal plane).

Acquisition of MR images

For logistic reasons, one patient received the first week of treatment at the 1.5 T MR-Linac and continued then at a conventional Linac (Versa HD™, Elekta AB, Stockholm, Sweden, 6 MV volumetric modulated arc therapy VMAT, image-guided RT IGRT with cone-beam CT CB-CT). For the purpose of this study, he was scanned every week at the 1.5 T Unity MR-Linac, and MRI scans were acquired for the simulation of the boost plans. For another patient, at the end of one treatment session during the third week it was impossible to acquire the post-treatment scan at the MR-Linac. Thus, for this patient only four boost plans were available. For the analysis, the missing dataset was replaced by the mean of the four adaptive boost plans. In total, 44 MRI datasets obtained at the 1.5 T MR-Linac were available.

GTV shrinkage and PTV variation

Tumor volume changes of the primary lesions throughout the course of fractionated irradiation was evaluated based on the 44 MRI scans (Fig. 3). A median shrinkage of the primary tumour (GTV) during the first week of treatment of 10.1 cm^3 (range 1.7–11.5) was observed. Over the entire radiation treatment course, a median shrinkage of the GTV of 15.7 cm^3 (range 6.2–35.5) was detected. This difference, i.e. between the GTV shrinkage during week one and the entire treatment course was statistically significant ($Z = -2.023$; $p = 0.043$).

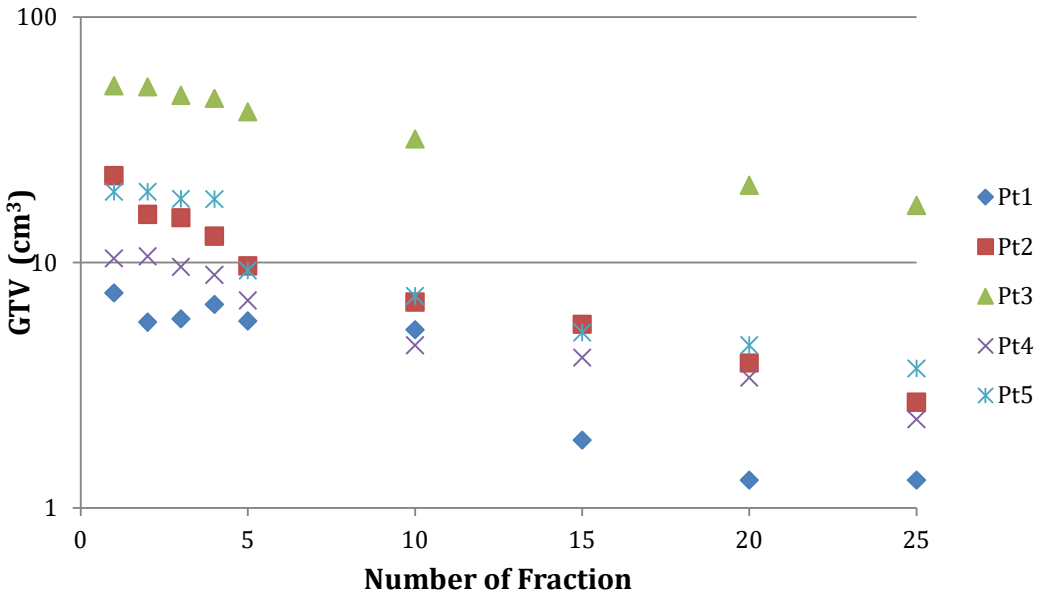

Figure 1 Gross tumor volume (GTV) during fractionated radiotherapy measured by T2 MRI acquired at the 1.5 T MR-linac. Fractionated radiotherapy consisted of 28 fractions over 5.5 weeks.

For the two boost strategies, i.e. up-front versus adaptive boost, the respective planning target volumes (PTVs) were generated by adding safety margins around the GTV (table 8a and b). When standard margins of 7/10 mm were used to generate the PTVs, the median PTVs in the up-front and adaptive boost strategy was 81.4 (range 43.2-181.3 cm^3) and 44.4 cm^3 (15-173.5 cm^3), respectively. When reduced margins of isotropic 3 mm were used, the corresponding median PTVs were 31.2 cm^3 for the up-front and 15 cm^3 for the adaptive boost strategy (ranges, 14.6-93.1 and 3-89.2, respectively). The reduction of the planning target volume resulted to be statistically significant in the adaptive strategy when both standard and reduced margins were used ($Z = -2.023$, $p = 0.031$). The adaptive boost strategy with reduced margins revealed the smallest PTV.

Table 8a Median PTV boost volumes with interquartile range for the individual patients with standard (7/10 mm) and reduced (3 mm) margins for upfront versus adaptive boost

	PTV Reduced Margins (IQR, cm^3)		PTV Standard Margins (cm^3)	
Patient	UpFront Boost*	Adaptive Boost*	UpFront Boost*	Adaptive Boost*
1	15.4 (18.6-14.6)	6.7 (18.6-3.2)	46.4 (52.4-43.2)	25.4 (52.4-16.4)
2	33 (45.2-25)	17.5 (45.2-10.3)	82.8 (109.5-68)	51.1 (109.5-37)
3	87.6 (89.2-75.9)	53.6 (89.2-38.6)	173.5 (173.5-153.3)	115.1 (173.5-89)
4	22.5 (24.1-17.3)	11.6 (24.1-7.9)	59.2 (62.3-48.9)	37.2 (62.3-28.5)
5	37.6 (38.8-21.6)	14.2 (38.8-11.2)	89.4 (90.6-58.1)	42.7 (90.6-36.8)

*UpFront Boost: median of the PTV boost volumes of the first five days of treatment; Adaptive Boost: median of the weekly PTV boost volumes. **Wilcoxon signed-rank test between median values of upfront and adaptive boost for all five patients.

Table 8b. Median PTV boost volumes with interquartile range for all five patients with standard (7/10 mm) and reduced (3 mm) margins for upfront versus adaptive boost

PTV	**UpFront Boost (cm^3) ***	**Adaptive Boost (cm^3) ***	***p* value****
Standard margins	81.4 (43.2-181.3)	44.4 (15-173.5)	***.031***
Reduced margins	31.2 (14.6-93.1)	15 (3-89.2)	***.031***

*UpFront Boost: median of the PTV boost volumes of the first five days of treatment; Adaptive Boost: median of the weekly PTV boost volumes. **Wilcoxon signed-rank test between median values of UpFront and Adaptive boost for all five patients.

Dosimetric comparison of the boost plans

In all plans an acceptable dose coverage of the PTV boost with at least 95% of the prescribed dose (15 Gy) covering at least the 98% of the PTV was achieved. For the dosimetric evaluation of the urinary bladder the mean dose (Dmean) and the volume of the organ receiving 40 Gy (V40) were derived from the dose

simulation. For both parameters, small but statistically not significant differences between the two boost strategies with regard to urinary bladder sparing were observed independent of the use of the standard or reduced margin. The dosimetric difference in the Dmean of the anal canal between the different boost strategies was also small (Fig 5a). For the two male patients, the dose to the penile bulb was kept with both strategies below the constraint of Dmean < 50 Gy. For the rectum, the following parameters were analyzed: Dmean, V60 and V65. For all three rectal parameters, a dosimetric advantage for the adaptive boost compared with the up-front was revealed (Fig. 5b, Table 9). When standard margins were used, the median Dmean, V60 and V65 for up-front and adaptive boost were 60.8 Gy, 69.1% and 32.8% vs 58.6 Gy, 55.5% and 29%, respectively ($Z = -2.023$, $p = 0.031$). The dosimetric advantage for the rectum by using an adaptive strategy was enhanced when reduced margins were applied: median Dmean, V60 and V65 for up-front and adaptive boost were 59.5 Gy, 59% and 29.9% vs 56.8 Gy, 41.2% and 24.8%, respectively ($Z = -2.023$, $p = 0.031$). Applying the QUANTEC recommendations for rectal bleeding (rectum V65 25% for grade 2 risk < 15% and grade 3 risk < 10% [53, 54]) three out of five patients would have been eligible for a boost irradiation if the adaptive planning strategy with reduced margin would have been used. In contrast, none of patients would have been eligible with the up-front boost strategy irrespective of the margin. Only one patient receiving the adaptive boost with standard margin would have not been eligible based on the dose constraints of the present planning study. Figure 4 shows an example of the MR imaging and simulated radiation dose distribution to illustrated that with an adaptive boost the surrounding organs at risk would have been better spared than with an upfront boost approach.

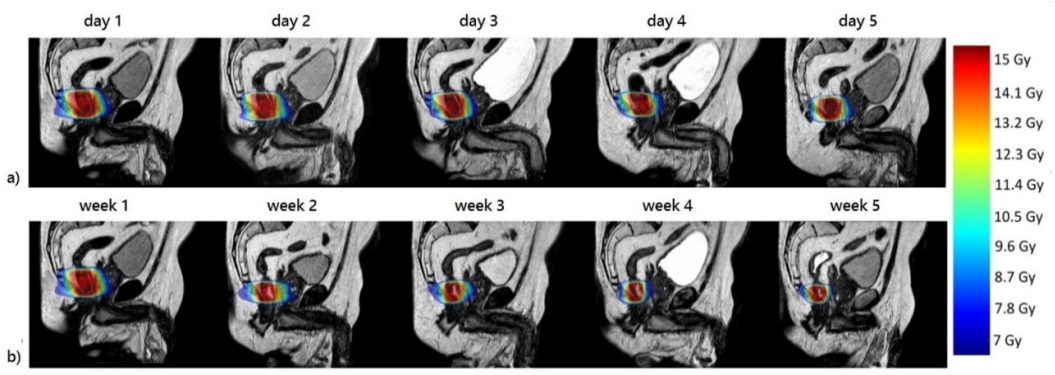

Figure 2 Sagittal views (T2w-6min images) of target volume (red lines) and dose distribution in the boost plans of patient 4. a) Up-Front boost with reduced margins on day 1 to 5 during week 1; b) Adaptive boost with reduced margins once per week during week 1 to 5. Only the dose distribution of the boost is shown. All patients received 50.4 Gy in 28 fractions to the pelvis.

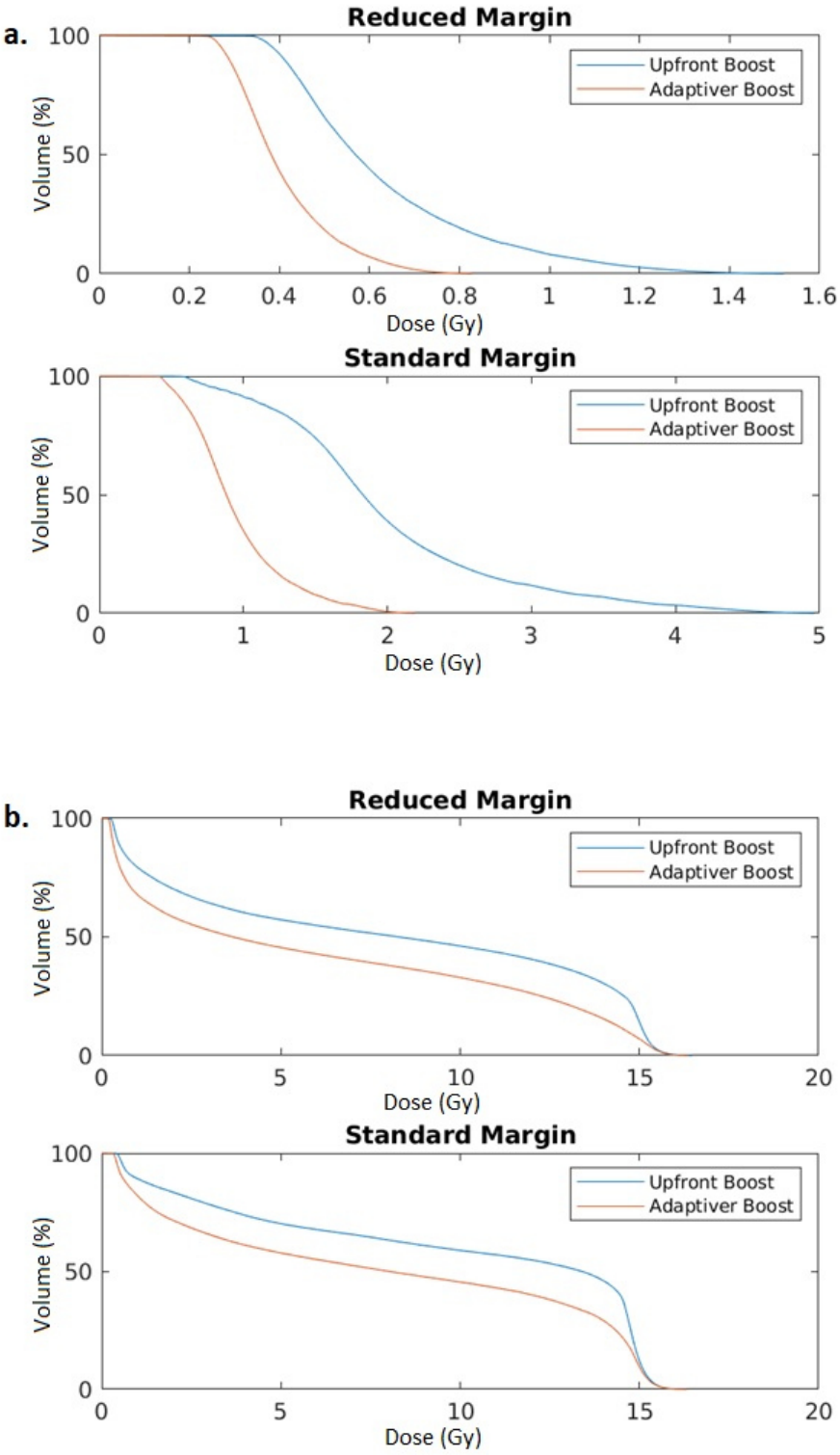

Figure 3 Dose-volume histograms (DVH) of the boost plans: a. DVH for anal canal and b. DVH for rectum, using standard and reduced margins.

Intra-fractional motion

For assessment of the intra-fractional tumor motion, a total of 41 fractions including 82 pre- and post-treatment MR scans was analyzed. The median time elapsed between the start of the pre-treatment scans and the end of post-treatment scan was of 13 minutes (range 9-32).

As shown in figure 6, in all evaluated patients investigated in this planning study an isotropic expansion of 3 mm to the GTV would lead to a 95% of coverage of the GTV during the treatment session.

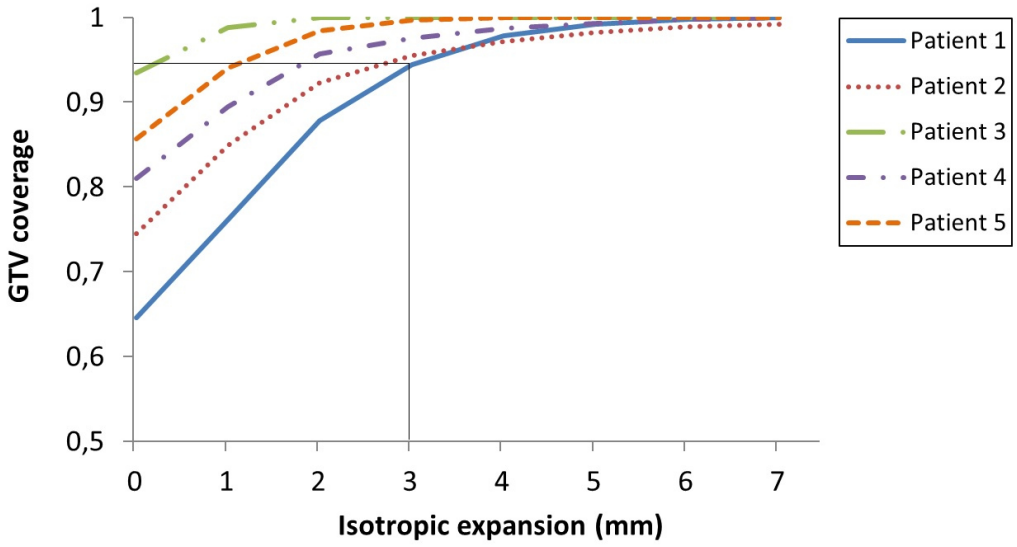

Figure 4 Isotropic expansion and relative GTV coverage during the treatment session.

Table 9 Dosimetric parameters to the rectum, bladder, and anal canal

	Reduced Margins					Standard Margins				
	UpFront Boost		Adaptive Boost			UpFront Boost		Adaptive Boost		
Parameter	Median	IQR	Median	IQR	*p* value*	Median	IQR	Median	IQR	*p* value*
Rectum										
Dmean§	59.5	58.6-61	56.8	56.1-58.8	***.031***	60.8	60.3-63.3	58.6	58.5-61.1	***.031***
V60†	59	49.5-66.7	41.2	32-55.2	***.031***	69.1	66.9-83.2	55.5	49.8-68.1	***.031***
V65†	29.9	27.5-37.4	24.8	17.1-29.4	***.031***	32.8	25.7-43.4	29	23.8-36	***.031***
Urinary bladder										
Dmean§	34.3	31.7-36	34.3	31.6-35.7	.125	34.7	32.4-36.9	34.4	32.1-36.1	.063
V40†	25.9	20.7-39.1	26	20.7-38.8	.063	26.5	22.1-39.8	26.1	22.4-39.2	.063
Anal Canal										
Dmean§	45.2	41.1-65.1	45	40.7-63.4	***.031***	45.3	42.1-65.8	45.2	41.2-64.5	***.031***

IQR, interquartile range, *Wilcoxon signed-rank test, § Values are reported in Gy, † Values are reported in % (percentage of volume of the OAR considered)

3.2. Case report

Intra-fractional motion with endorectal gel filling

To prepare the first clinical application at the MR-Linac and using rectal filling with ultrasound gel, tumor shifts in diagnostic MRI scans performed with gel filling were retrospectively examined. For this analysis, ten diagnostic pelvic MRI scans of ten rectal cancer patients acquired after rectal application of ultrasound gel in the Department of Diagnostic Radiology were used. The median time between the first and the last morphological scans (T2w and T1w) was 25 minutes (interquartile range IQR 20.5-27). The median 95% Hausdorff distance between the two structure sets was 5.2 mm (IQR 4.08-6.42). On average, an isotropic expansion of 4 mm of the GTV would have been sufficient to ensure the 95% of target coverage. In nine of the ten cases an expansion of 5 mm would have been sufficient to achieve a target coverage >94.3%.

Treatment and toxicity

From April to June 2021 the patient received a radiotherapy treatment with 45/50 Gy in 25 fractions (ICRU, prescription to the PTV 45 Gy, PTV 50 Gy) and concomitant chemotherapy without any delays or dose modifications. A total of three online adaptive boost fractions to the primary tumor (GTV) were given. No further dose escalation was performed as considerable tumor shrinkage had already been observed at the second boost treatment. It was therefore decided to skip the boost fraction in week three and to apply one more boost to potential residual GTV in week four. The total treatment time of the three online adaptive boost fractions, i.e. the time elapsed from the pre-treatment imaging until the end of the radiation delivery, was of 22:41, 22:06 and 23:56 minutes, respectively. Tumor volume was 18.37 cm^3 at the first, 7.93 cm^3 at the second and 4 cm^3 at the third boost fraction. After the first fraction the margin was reduced anteriorly from 5 mm to 2 mm. This was due to continuous filling of the bladder during treatment and a shift in this direction appeared unlikely. Based on the anatomy on the pre-treatment MRI, in the online adaptive plans the D95% for the GTV was

3.0 Gy in all three boost fractions. We also evaluated the GTV dose coverage based on the post-treatment MRI, and thus considering any displacement of the target volume occurred during the radiation delivery (intrafractional motion). The coverage was still optimal with a D95% in all three boost fractions of 2.93 Gy, 2.85 Gy and 2.99 Gy.

The treatment was very well tolerated as reflected by the treatment experience questionnaire (Table 10). At the end of treatment, the patient reported no more than PRO-CTCAE grade 1 gastro-intestinal toxicity and grade 1 fatigue. No other toxicities were reported.

The first follow-up with pelvic MRI performed in August, 10 weeks after treatment completion, showed a good tumor response to therapy with a minimal residual wall thickening. These findings were confirmed in the proctoscopy. At this time point, the patient had reported no late toxicity.

Table 10 Patient reported treatment experience

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
I found the treatment position comfortable	3	3	3	3	3	3
I found the treatment bed comfortable	3	3	3	3	3	3
I found it easy to stay still and maintain the treatment position	3	3	3	3	3	3
I wanted to come out of the machine during my treatment	0	0	0	0	0	0
I felt calm during my treatment	3	3	3	3	3	3
I needed more detailed information before my treatment	0	0	0	0	0	0
I found the noise in the room easy to tolerate	3	3	3	3	3	3
I found the lighting in the room easy to tolerate	3	3	3	3	3	3
I found the time taken for the treatment easy to tolerate	3	3	3	3	3	3
I felt dizzy during my treatment	0	0	0	0	0	0
I felt dizzy immediately after my treatment	2	0	0	0	0	0
I felt hot during my treatment	2	0	0	0	0	0
I felt tingling sensations during my treatment	0	0	0	0	0	0
I experienced a metallic taste during my treatment	0	0	0	0	0	0
I needed more communication from staff during my treatment	0	0	0	0	0	3
I forced myself to manage the situation	0	0	0	0	0	0
I found listening to the music helpful whilst having my treatment	3	3	3	3	3	3
I understand the procedure	2	3	3	3	3	3

0 = Fully disagree, 1 = rather disagree, 2 = rather agree, 3 = fully agree

Plan comparison with and without endorectal gel filling

As secondary goal was to evaluate this dose escalation approach if the use of the endorectal filling would result in better organ sparing when compared to a standard setup with empty rectum. For this purpose, based on the MR scans without endorectal filling acquired at the MR-Linac during the delivery of the base plan, we generated offline a new boost plan with the same dose prescriptions as for the delivered plan. With endorectal filling the dose to the rectal wall was found considerably reduced mostly in the high dose range. The volume of the rectal wall receiving the 100% of the prescribed dose (V100%) was reduced from 46% to 24%, the V95% from 61% to 33% and the V50% from 92% to 77%.

Figure 7 shows a comparative visualization of the dose distribution with and without endorectal filling.

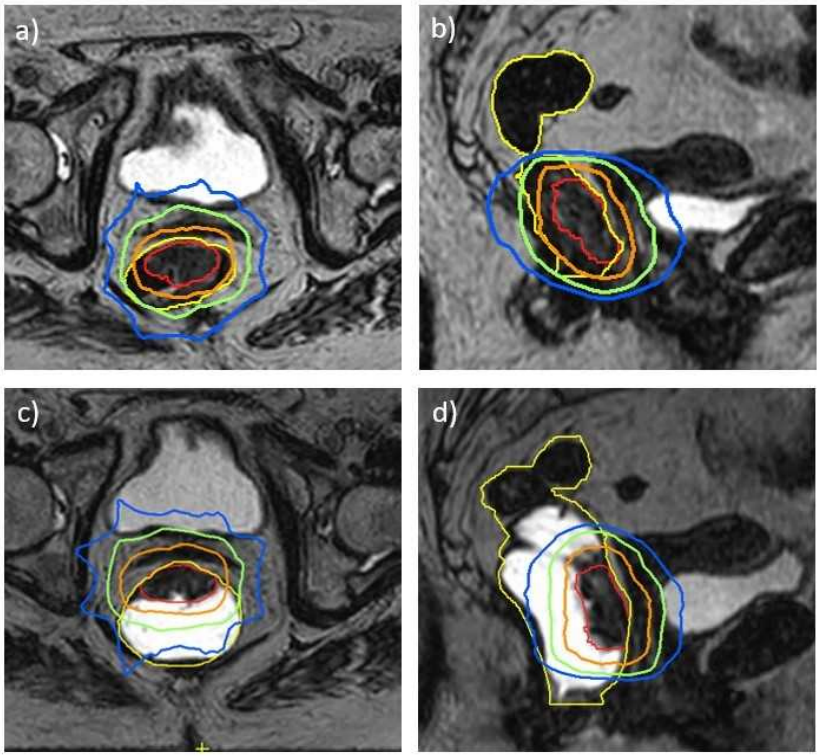

Figure 5 Dose distribution of a 3 Gy boost plan on the 1.5 T MR-Linac without (a and b) and with rectal ultrasound gel filling (c and d). Yellow - rectum, red: primary tumor, orange - 95% Isodose, green - 70% isodose, blue - 50% isodose.

Follow-up

A follow-up MRI was performed 3 months after to end of the radiation treatment: a good response to treatment was described with a residual thickening of the rectal wall, without signs of local or distant recurrence. The treatment was well tolerated without ≥ 2 late toxicities.

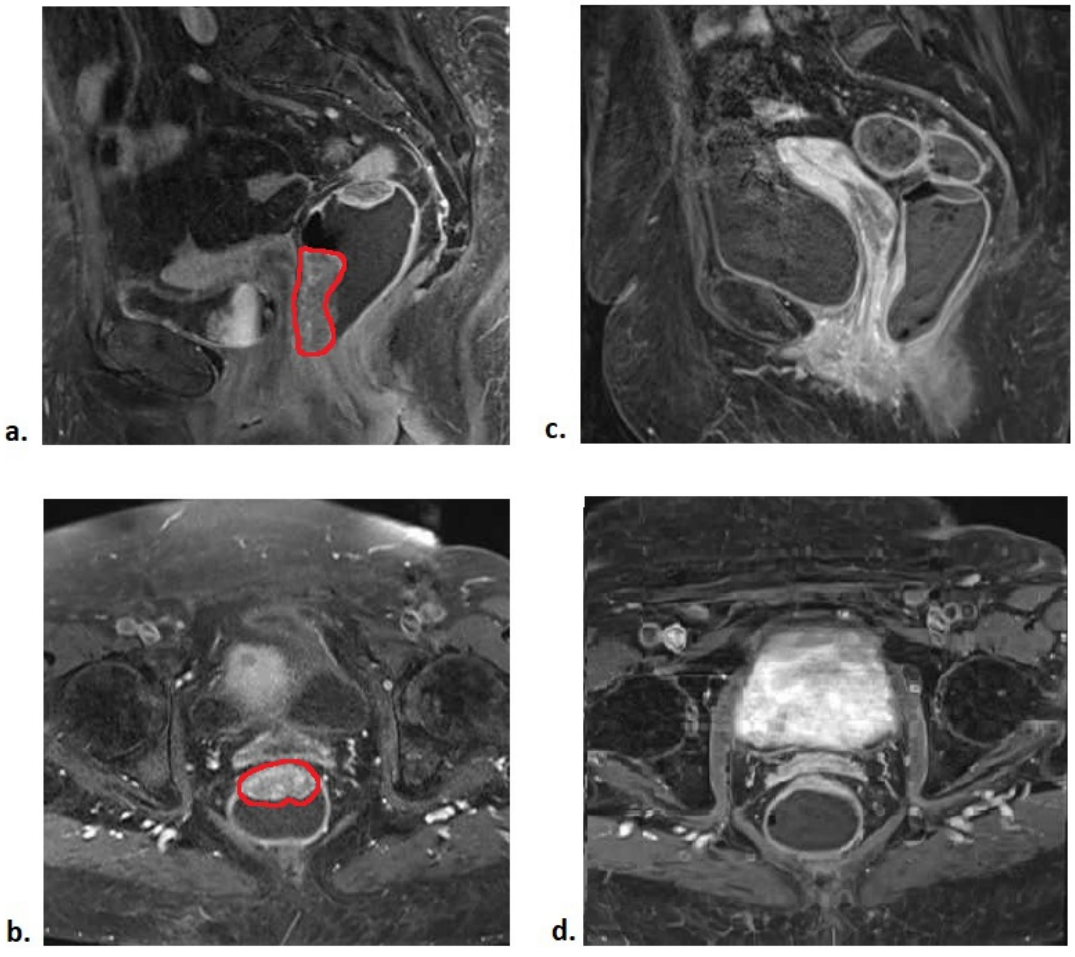

Figure 6 Diagnostic pelvic MR images in sagittal and transversal view, at the time of diagnose (a and b) and three months after treatment (c and d). In red the gross tumor volume (GTV) in the pre-treatment MRI scan.

4. DISCUSSION

The purpose of the present work was to define the optimal schedule for dose escalation to the primary tumor volume in rectal cancer patients by using the advantages offered by MR-guided radiotherapy. It was hypnotized that an adaptive boost exploiting both the shrinkage of the rectal tumor and the reduction of the safety margins would lead to superior sparing of adjacent normal tissues.

Several studies suggested that pCR after neoadjuvant CRT is associated with better outcome in terms of local and distant control, DFS and OS. In a pooled analysis conducted by Maas and colleagues the 5-year DFS in patients with pCR after CRT was statistically superior compared to those without pCR (83.3% vs 65.6%, respectively) [55]. Data from this analysis supported the independent prognostic value of pCR. It may be speculated that the association of pCR and prognosis may be explained by a biological link between sensitivity to radiochemotherapy and the risk of developing distant metastases [56]. The latter has been shown to be the major contributor to OS. Furthermore, whether strategies that increase pCR may affect OS remains controversial. Irrespective of the potential impact of pCR on OS, the omission of surgery in patients with complete response after neoadjuvant radiochemotherapy appears attractive as it may avoid significant morbidity such as sexual and urinary disfunction and anastomotic leaks [57]. The omission of surgery in selected patients with complete response to neoadjuvant CRT is recognized since 2004 as an oncologically safe option [41]. However, this approach requires that local regrowth or persistent disease is early detected for timely surgery. This implies more frequent and careful surveillance than in routine patients. Currently, no robust clinicopathological factors have been identified to predict cCR or pCR. Such factors would be ideal to design better individualized management and care plans. In addition, no standard has been identified to increase the likelihood of cCR after neoadjuvant treatment. In clinical trials different approaches with the aim to increase cCR and pCR have been investigated, e.g. the prolongation of

the interval between neoadjuvant CRT and surgery [24], hyperthermia [58] or the enhancement of chemotherapeutic agents [59].

Recently, total neoadjuvant therapy (TNT) for rectal cancer patients was introduced as a novel therapeutic approach. It incorporates chemotherapy with CRT both given prior to surgery. In the PRODIGE 23 trial, patients with stage cT3-4 rectal cancer were randomized to receive either standard treatment (CRT, surgery, and adjuvant chemotherapy) or, in addition to it, neoadjuvant chemotherapy with FOLFIRINOX. The first results published in April 2021 showed a significant reduction of the incidence of distance metastases and a higher 3-years DFS for the experimental arm compared to the standard arm (76% vs 69%, respectively). Moreover, pathological complete response rate, tumor regression, and the number of metastatic regional lymph nodes were also improved in the experimental arm. However, even if not statistically significant, serious adverse events occurred with a higher percentage compared to the standard arm (27% vs 22%, respectively) [60]. In analogy to the PRODIGE 23 trial, in the RAPIDO trial patients included in the experimental arm received short-course radiotherapy, consisting in 5 daily fractions of 5 Gy over a maximum of eight days followed by either six cycles CAPOX or nine cycles FOLFOX4 prior to surgery. The cumulative probability of distant metastases was lower in patients receiving TNT than in those in the standard arm (20% vs 26.8%, respectively) and the pCR rate was higher (28% vs 14%, respectively). In the experimental arm, toxicity ≥ grade 3 occurred in 48% of patients compared to 25% of patients in the standard arm [37]. Based on the results of these recent studies, TNT is considered nowadays a promising approach in patients with high risk rectal cancer. On the other hand, intensified systemic treatments result in more toxicity as well as long-lasting impairments in QoL especially due to polyneuropathy [61].

Besides the intensification of chemotherapy as in the above-mentioned studies, the association between high radiotherapy doses and response rates has been previously studied. A meta-analysis conducted by Burbach et al. demonstrated that radiation dose escalation may be a viable strategy to increase tumor response rate without increasing severe acute ≥ grade 3 toxicity [62]. According

to a previously published mathematical radiation dose-response model [63], relatively high radiation doses i.e., above 60 Gy normalized to 2 Gy per fraction, seem to be necessary to achieve a clinically relevant gain in the pCR rate. However, since toxicity is of particular concern when radiation dose is escalated, a precise dose delivery to the tumor avoiding adjacent normal tissues is crucial and leads to several challenges. Firstly, the anatomy of the rectum and consequently of the tumor and the surrounding tissues undergoes relevant day-to-day changes in position (*inter-fractional motion*), shape, and volume. Furthermore, changes in the position of the tumor during the treatment session of several minutes, i.e., *intra-fractional motion*, must be considered as well. Therefore, safety margins for position and motion uncertainties need to be added to ensure adequate target coverage. On the other hand, too large margins increase the dose and volume of irradiated normal tissues (organs at risk, OAR) which then correlates with the development of toxicity and loss of function, e.g. sphincter function in lower rectum tumors. Therefore, radiation dose escalation of rectal cancer to substantially increase pCR requires high precision to allow as small as achievable safety margins to reduce the risk of toxicity without jeopardizing target coverage. Secondly, during the course of fractionated irradiation tumors often shrink considerably as they respond to treatment. In a prospective analysis by van den Begin et al., MRI scans of 15 patients acquired before therapy, weekly during five weeks of standard CRT and before surgery were evaluated. A significant tumor volume reduction was observed in all but one patient. The latter experienced local progression prior surgery. In the entire cohort, a reduction of 53.7% of the initial tumor volume was observed in the last week of therapy. Regarding velocity of shrinkage, the authors found a faster tumor volume reduction during the first three weeks of treatment with 26% of tumor volume reduction per week independent of the absolute initial tumor volume [44]. Thirdly, radiation dose escalation requires optimal timing, schedule, as well as delivery technique securing highest target coverage without increasing of dose to the OARs. Various strategies for radiation dose escalation for rectal cancer have been studied. Currently, two on-going randomized phase II clinical trials, the WW3 and the APHRODITE trial, investigate dose escalation up to 62

Gy [64, 65]. For the application of the escalated local boost dose to the primary tumor both trials use CB-CT-guided simultaneous integrated boost (SIB) technique with total radiation doses of 50.4 Gy to the elective volume and 62 Gy to the tumor volume in 28 fractions. In 2020, the results of the RECTAL BOOST trial were published. In this randomized phase II trial, locally advanced rectal cancer patients were randomized to receive neoadjuvant CRT with standard dose (50 Gy in 25 fractions over 5 weeks) with concurrent capecitabine or to receive a escalated radiation dose with boost to the primary tumor followed by standard neoadjuvant CRT as in the standard arm. Similar to the upfront boost strategy evaluated in the present planning study, the escalated dose as boost consisted of 15 Gy in five daily fractions during the first week of treatment followed by standard CRT of 50 Gy in 25 fractions. Target volume was delineated on planning CT scan informed by a staging MRI scan. The primary endpoint, i.e. increase of cCR rate in the experimental arm, was not met. However, an increased rate in near and complete clinical response as well as in sphincter preservation was observed in patients who received the dose escalation. However, as the authors also state, in the boost plan the dose constraints to the OARs were prioritized over the boost dose. Thus, in the experimental arm the dose often had to be reduced. The resulting median dose was 58.9 Gy, i.e. more than 10% less than the planned dose of 65 Gy as defined per protocol [45].

MR-Linac systems are hybrid devices that combine an MRI scanner with a linear accelerator [66]. They have been recently introduced in clinical practice and have now been established at an increasing number of radiotherapy centers worldwide. The new concept of an online adaptive MR-guided radiotherapy (MRgRT) is based on the capacity of the MR-Linac system to acquire daily in-room images in treatment position with high soft-tissue contrast allowing high precision without implanted fiducial markers. Based on daily MR scans, those systems allow an online adaptive workflow by re-definition of target volumes and organs at risk based on the anatomy of the day, re-optimization of treatment plans just prior delivery and with cine-MR sequences a real-time motion monitoring of the target while treatment beam is on. Based on this new technology, it has been proposed that safety margins might be reduced. In addition, sequential MR scans

during the course of radiotherapy is well suited to capture treatment response not only as tumor shrinkage but also with functional imaging indication early response which may allow repetitive individualized treatment adaptation [67].

Based on its advantages, MR-Linac systems provide a promising solution to address the challenges for precise dose escalation of rectal cancer. In the present planning study, it was hypothesized that an adaptive MR-guided dose escalation to the rectal tumor may result in better sparing of the OARs than an up-front boost due to the possibility to account for tumor shrinkage during the course of fractionated radiotherapy. It is expected that shrinkage in the up-front boost is less pronounced than in the adaptive boost strategy where the boost is spread out over 5 weeks. As a first step to test this hypothesis, the intra-fraction tumor motion by using pre-treatment and post-treatment MRI scans during a radiation session was assessed to estimate the safety margin for adequate target coverage. An isotropic expansion of 3 mm was found which is smaller than usual in clinical practice. Based on these observations, compared four different boost strategies were compared:

1. Up-front boost with standard PTV margins
2. Up-front boost with reduced PTV margins
3. Adaptive boost with standard PTV margins
4. Adaptive boost with reduced PTV margins

The results suggest that both, an adaptive boost throughout five weeks of treatment and a margin reduction at the MR-Linac resulted in the most effective sparing of the rectum without target miss. In the RECTAL BOOST trial, the boost application was guided by CB-CT which offers less soft tissue contrast than standard CT or MRI. To compensate for this limitation, larger safety margins to ensure appropriate target coverage are necessary. PTV margins used in the RECTAL BOOST trial (7 mm laterally, 11 mm antero-posteriorly and 13 mm cranio-caudally) were similar to the standard margins adopted in the present analysis (7 mm laterally, 10 mm in all other directions). Moreover, in the RECTAL BOOST trial the boost fractions were applied in five consecutive days at the

beginning of treatment with target volumes defined on the off-line staging MRI scan. As result, larger volumes were treated and to avoid excess toxicity, target coverage was compromised and consequently the dose escalation level was not reached as planned. As predicted no increase in toxicity was observed at one year after dose escalation. The rate of grade ≥ 3 toxicity was comparable between the two groups: 9.4% in the boost group versus 7.8% in the control group. These results were in line with the data published by Burbach et al in the retrospective meta-analysis of rectal dose escalation [62].

Normal tissue complication probability (NTCP) models are dose-dependent mathematical models able to predict radiation-induced morbidities considering the specific cell biology of a considered organ. Regarding rectal cancer, NTCP models for late rectal toxicity have not been reported. Validating a predictive model for rectal and anal toxicity following radiation therapy for rectal cancer has limits. First, rectal function is already compromised at the time of diagnose. The majority of patients present before the beginning of treatment rectal symptoms e.g., bleeding, incontinence, pain and in some of them a preventive colostomy is carried out when symptoms of stenosis are present. Second, the standard therapeutic path also includes major surgery, that itself is associated with impairment of rectal and anal function. As the Watch-and-Wait strategy in patients with complete clinical response is becoming widespread, it becomes essential to preserve maximum functionality and maintain optimal levels of QoL. With the intent to escalate the total radiation dose to the rectum up to 60 Gy, to define dose-constraints for a boost plan it is necessary to draw on data from radiation treatment of other cancer entities. For the treatment of prostate cancer average doses of 60-80 Gy, depending on the intent of therapy, i.e., primary or adjuvant, are required. There is a large body of evidence derived from prostate cancer radiotherapy that recommends dose-volume constraints to minimize the risk of late toxicity. In a prospective study of rectal dose escalation using brachytherapy, the rectal bleeding was one of the dominant late toxicities after 5 years of follow-up [68]. Fiorino et al and the QUANTEC (quantitative analysis of normal tissue effects in the clinic) recommendations provide the following dose–volume

constraints to keep the risk of grade ≥ 3 late rectal bleeding below 10% and grade ≥ 2 below 15% [53, 54]:

- The volume of rectum receiving 60 Gy must be kept below 35-45% (V60 ≤ 35-45%)
- The volume of rectum receiving 65 Gy must be kept below 25% (V65 ≤ 25%)

In our experience, only using both an adaptive boost strategy and reduced margins it was possible to respect the above-mentioned dose-volume constraints. Basing the eligibility for a dose escalation on the QUANTEC recommendations, no patients would have been eligible for an upfront boost strategy. Further, three patients out of five would have been eligible for the boost if an adaptive strategy and reduced margins would have been used.

For the treatment of rectal cancer patients, the MRgRT leads as previously discussed to many advantages. However, the incorporation of an MRI scanner with a linear accelerator brings major challenges, among which the influence of the magnetic field on the dose deposition.

The interaction of the primary photon beam with matter distant from the target generates secondary electrons, which are influenced by the magnetic field. The Lorentz force F_L, or electromagnetic force, derives from the combination of electric and magnetic force:

$$F_L = -e(E + v\ x\ B)$$

were E is the strength of the electric field, B the magnetic field flux, $-e$ the charge of electron and v its velocity. The generated secondary electrons in a magnetic field experience, consequently, a change of trajectory, which results in a different dose deposition in the patient. In proximity of low-density tissues or air, secondary electrons are directed in a circular path. This phenomenon, called electron return effect (ERE), poses particular concern. Electron exiting from patients´ surface and returning back after crossing a density boundary, may cause an overdosage

close to the entrance point. Regarding the treatment of rectal cancer patients, the overdosage on the rectal mucosa caused by the presence of gas in rectum not accounted during the planning could increase the risk of toxicity [69]. In a recent study, Shortall et al described the dose perturbation during MRgRT due to the ERE in the presence of air cavities. The authors reported a cumulative dose perturbation in the order of 60% to the rectal wall if the rectal gas was not considered in the plan generation. Nevertheless, this dose perturbation could be significantly reduced if more beams are used, namely of two thirds in a path of a five-beams plan. Moreover, the authors state that this phenomenon is negligible if air cavities have small diameters (≤0.5 cm) [70]. In our analysis, all the boost plans were generated with a 9-beams template and, moreover, in our cohort of patients no case of significant rectal air filling was noticed. Furthermore, Shortall et al investigated in twenty-two cervical, bladder and prostate patents with a total of 563 MRI scans the stability of the rectal gas during a time frame of 20-25 minutes. The authors found that during a MRgRT fraction the rectal gas is likely to remain stable and therefore the dose perturbation after the daily re-planning is low [70].

Therefore, although limited by the small number of included patients, the data obtained from our planning study suggest that an adaptive boost strategy exploiting the tumor shrinkage and reduce margins allow a safer dose escalation to the primary rectal tumor volume and, at the same time, a better sparing of the rectum. Hence an MRI guided treatment represents a solution for those challenges deriving from a dose escalation to the rectum. These findings were subsequently translated into a successful first-in-human application [47]. In the described clinical case, the indication for a rectal boost was given as an alternative treatment approach in order to avoid a second major surgery. With the aim to obtain nevertheless an optimal local control without spoiling the QoL and therefore without causing too much toxicity, we decide to exploit the advantages of an online adaptive MR guided for the rectal dose escalation. For the delivery of the boost fractions, one day per week, we decided to use sonography transmission gel as endoluminal contrast agent.

Rectal distension using ultrasound gel filling in the diagnostic MR imaging for the staging of rectal cancer is controversial. Some authors consider the rectal distension an important tool to depict the rectal lesion within the wall and its extension [71]. On the other, its role in diagnostic imaging remains controversial since, by pushing the rectal walls into the mesorectum, errors in the depiction of the MFR involvement could be made. Moreover, the ultrasound gel filling could increase the apparent diffusion coefficient (ADC) values, an imaging biomarker of tumor aggressiveness [72, 73]. Our hypothesis behind its use in the reported clinical case was that, for an MR-guided dose escalation to the primary rectal tumor volume those that are disadvantages of a rectal distension in a context of staging, may be potential advantages for an online adaptive boost. By using ultrasound gel filling as endorectal contrast agent, it is possible to clearly distinguish the primary lesion to the rectal lumen and fecal material. This allowed a fast GTV definition in less than two minutes during every boost fraction, while the patient was on the treatment table. Besides, the rectal distension resulted in a distancing of the irradiated volume from the OARs including the surrounding healthy rectal mucosa and therefore in a considerable reduction of the dose to the normal tissue. By comparing the boost plans with and without rectal gel filling, we found that the amount of healthy rectal mucosa receiving the prescribed dose was reduce by almost a half when the endorectal gel filling was used (46% vs 24%).

Since no data about the stability of the endorectal gel filling during a time frame of at least 20 minutes was available in literature and due to the concern, that its use could have result in major shift of the primary lesion during the treatment session, first we analyzed the tumor motion in ten rectal cancer patients underwent to diagnostic pelvic MRI scan with endorectal gel filling. The median time between the two analyzed time point was of 25 minutes, which is in line in our experience with the duration of an online adaptive workflow, and small margins i.e., of 4 mm, were sufficient to ensure target coverage.

5. SUMMARY

In the treatment of rectal cancer, efforts are made to increase the rate of clinical complete response to chemoradiotherapy. The avoidance of major surgery and consequently of associated morbidity but maintaining at the same time similar local control rates, is an attractive concept. Dose escalation to the primary rectal tumor appears to be a viable solution. However, for a precise and safe dose escalation many challenges must be addressed. Recently, the new concept of online MR guided radiotherapy has been introduced and established worldwide at a number of radiotherapy centers. Based on MR-imaging with high soft tissue contrast, daily online plan adaptation, individual margin reduction and motion management, these new hybrid systems appear an attractive solution to overcome limitations of conventional image-guided radiotherapy for dose escalation to the rectal tumor. In the presented analyses, the potential of online adaptive MRgRT using different boost strategies were compared on the basis of dose simulations for optimal tissue protection and tumor coverage. The data suggest that an adaptive boost strategy during long course CRT exploiting tumor shrinkage and reduced margins is superior compared to an upfront strategy and larger margins. The data from the simulation study motivated the Tübingen MR-Linac team to translate this adaptive dose-escalation concept into a first-in-human application. For the first time, feasibility and promising early outcome was observed in a primary non-surgical management patient was documented. This was supported by a novel approach to use rectal filling with ultrasound gel which enhanced visibility of the tumor and facilitated spatial separation of the tumor from non-involved normal rectum and thereby potentially decrease the risk of toxicity. Overall, the response-adaptive boost concept and the rectal filling approach support the further development of radiation dose escalation to increase clinical complete response and thereby the rate of patients who can be managed without surgery. Prospective trials are under preparation including novel imaging biomarkers for early response-adaptive MR-guided radiotherapy.

6. ZUSAMMENFASSUNG

Beim Rektumkarzinom wird derzeit versucht, die Rate an klinischen Komplettremissionen nach Radiochemotherapie zu steigern. Die Vermeidung der Operation und der damit verbundenen Nebenwirkungen bei gleicher lokaler Tumorkontrolle stellt ein attraktives Konzept dar. Die Eskalation der Strahlendosis auf den Primärtumor im Rektum ist dabei ein Ansatz, wobei hier Präzision und Sicherheit große Herausforderungen darstellen. Die Echtzeit-MR-geführte Strahlentherapie (MRgRT) ist ein neues Konzept, dass an einigen Standorten weltweit bereits etabliert wurde. Basierend auf der MR-Bildgebung mit hohem Weichteilkontrast, täglicher Echtzeit-Planadaptation, reduzierten Sicherheitssäumen und Bewegungskontrolle, stellen die MR-Hybrid-Systeme eine attraktive Lösung zur Überwindung der Limitationen der konventionellen bildgeführten Strahlentherapie zur Dosiseskalation beim Rektumkarzinom dar. In der vorliegenden Arbeit wurde das Potenzial der Echtzeit-adaptiven MRgRT mit zwei unterschiedlichen Boost-Strategien auf Basis von Dosissimulationen für die optimale Normalgewebsschonung und Tumorerfassung analysiert. Die Ergebnisse legen nahe, dass die adaptive Boost-Strategie mit Erfassung der Tumorschrumpfung während einer 5-wöchigen Radiochemotherapie und gleichzeitiger Reduktion der Sicherheitssäume besser als der sogenannte Upfront-Boost mit größeren Sicherheitssäumen ist. Diese Daten haben dazu geführt, dass das Tübingen MR-Linac Team dieses Konzept in einer first-in-man Studie erstmals erfolgreich klinisch eingesetzt hat. Die ersten Ergebnisse zeigen eine Machbarkeit und gute Frühergebnisse zur Verträglichkeit und Wirksamkeit. Zusätzlich konnte ein neuer Ansatz mit rektaler Füllung mittels Ultraschal-Gel angewandt werden, der die Sichtbarkeit des Tumors und die Distanzierung von Tumor und normaler Rektumschleimhaut und damit der Toxizität unterstützt. Insgesamt ist das Konzept der response-adaptiven MRgRT zur Dosiseskalation für eine höhere rate an klinischen Komplettremissionen und damit weniger Operationen sehr vielversprechend. Dazu befinden sich prospektive Studien in Vorbereitung, die auch neue imaging Biomarker für die frühe response-adaptive MRgRT Strahlentherapie beinhalten.

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8. ERKLÄRUNG ZUM EIGENANTEIL

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Ich versichere, das Manuskript selbstständig verfasst zu haben und keine weiteren, als die von mir angegebenen Quellen, verwendet zu haben.

Die Daten der vorliegenden Promotionsschrift sind in zwei Manuskripte eingeflossen, in welchen ich als Co-Autor aufgeführt bin.

Tübingen, den 19.12.2021 Monica Lo Russo

9. PUBLICATIONS

The results of the present studies have been published this year in the following original articles:

Authors: Pierluigi Bonomo, Monica Lo Russo, Marcel Nachbar, Simon Boeke, Sergios Gatidis, Daniel Zips, Daniela Thorwarth, Cihan Gani.

Title: 1.5 T MR-linac planning study to compare two different strategies of rectal boost irradiation

Journal: Clinical and Translational Radiation Oncology

Year: 2021

Authors: Cihan Gani, Monica Lo Russo, Simon Boeke, Daniel Wegener, Sergios Gatidis, Sarah Butzer, Jessica Boldt, David Mönnich, Daniela Thorwarth, Konstantin Nikolaou, Daniel Zips, Marcel Nachbar.

Title: A novel approach for radiotherapy dose escalation in rectal cancer using online MR-guidance and rectal ultrasound gel filling – Rationale and first in human

Journal: Radiotherapy and Oncology

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