Clinical Oncology 35 (2023) e135–e142

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Understanding the Benefit of Magnetic Resonance-guided Adaptive Radiotherapy in Rectal Cancer Patients: a Single-centre Study

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Abstract

Aims: Neoadjuvant chemoradiotherapy followed by surgery is the mainstay of treatment for patients with rectal cancer. Standard clinical target volume (CTV) to planning target volume (PTV) margins of 10 mm are used to accommodate inter- and intrafraction motion of target. Treating on magnetic resonance-integrated linear accelerators (MR-linacs) allows for online manual recontouring and adaptation (MRgART) enabling the reduction of PTV margins. The aim of this study was to investigate motion of the primary CTV (CTVA; gross tumour volume and macroscopic nodes with 10 mm expansion to cover microscopic disease) in order to develop a simultaneous integrated boost protocol for use on MR-linacs.

Materials and methods: Patients suitable for neoadjuvant chemoradiotherapy were recruited for treatment on MR-linac using a two-phase technique; only the five phase 1 fractions on MR-linac were used for analysis. Intrafraction motion of CTVA was measured between pre-treatment and post-treatment MRI scans. In MRgART, isotropically expanded pre-treatment PTV margins from 1 to 10 mm were rigidly propagated to post-treatment MRI to determine overlap with 95% of CTVA. The PTV margin was considered acceptable if overlap was >95% in 90% of fractions. To understand the benefit of MRgART, the same methodology was repeated using a reference computed tomography planning scan for pre-treatment imaging.

Results: In total, nine patients were recruited between January 2018 and December 2020 with T3a-T4, N0–N2, M0 disease. Forty-five fractions were analysed in total. The median motion across all planes was 0 mm, demonstrating minimal intrafraction motion. A PTV margin of 3 and 5mm was found to be acceptable in 96 and 98% of fractions, respectively. When comparing to the computed tomography reference scan, the analysis found that PTV margins to 5 and 10 mm only acceptably covered 51 and 76% of fractions, respectively.

Conclusion: PTV margins can be reduced to 3–5 mm in MRgART for rectal cancer treatment on MR-linac within an simultaneous integrated boost protocol.

Key words: Adaptive radiotherapy; MR-linac; MRI; rectal cancer

Introduction

Colorectal cancer is the third most common cancer in the UK, with rectal cancer accounting for >50% of cases [1]. Most patients with locally advanced rectal cancer (stage II and above [2]) in the UK are treated with neoadjuvant chemoradiotherapy (nCRT) to a total dose of 45 Gy/25 fractions to the pelvis using conformal radiotherapy with daily chemotherapy [3] followed by surgery [4]. A sequential boost of 9 Gy/five fractions to the primary target and macroscopic nodal disease can be added, increasing the total dose to 54 Gy/30 fractions [3] with the aim to improve the response to treatment. Increasing the radiotherapy dose delivered to the primary target can potentially increase the rate of complete pathological response (cPR) [5–8]; cPR is an independent prognostic factor for overall survival, local recurrence and disease-free survival [9–13]. Overall survival rates for patients who achieve cPR compared with non-cPR are >87% [11] versus 50–60% [12,14] at 5 years, respectively. However, with current fractionation schedules, the proportion of patients who achieve cPR is small; at about 15–25% [15].

With the introduction of intensity-modulated radiotherapy and image-guided radiotherapy homogeneity of

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https://doi.org/10.1016/j.clon.2022.10.008

dose to the target volume has improved, as well as improving conformality, reducing doses to organs at risk (OARs) [16]. Using intensity-modulated radiotherapy also enables boost to be delivered simultaneously with pelvic treatment, as shown by Owens *et al.* [17]; where the primary clinical target volume [CTVA; gross tumour volume (GTV) and macroscopic nodes with 10 mm expansion to cover microscopic disease] is treated to a total dose of 52.5 Gy and the remaining pelvis (CTVB: mesorectal, obturator, presacral and internal iliac nodes) is treated to 45 Gy, within 25 fractions. Using this technique, 23.9% of patients were found to achieve cPR [17].

However, there is scope for further improvement of cPR rates. Greater escalation of radiotherapy dose is limited due to large planning target volume (PTV) margins required to accommodate for inter- and intrafraction motion of the target volume [18–21]. Adaptive radiotherapy strategies, in particular online manual recontouring, play an important role in managing motion during radiotherapy for rectal cancer, with the aim of reducing PTV margins [22,23]. With the advent of magnetic resonance integrated linear accelerators (MR-linacs), daily online MR-guided adaptive radiotherapy (MRgART) can mitigate the effects of interfraction motion by daily recontouring [24] and re-optimisation of a plan based on the position of the target and OARs on the day [25,26]. Furthermore, tumour target is better visualised on MRI, allowing greater confidence in delineation and reduced interobserver variation [27].

Initially, treatment of rectal cancers on certain MR-linacs was limited to delivering only sequential boost to the primary target volume due to restrictions in the field length of the treatment beam of 22 cm [28]. Whole-pelvis treatment can now be delivered in rectal cancer [25], enabling a move towards a simultaneous integrated boost (SIB) protocol for rectal cancer patients using MRgART. Previously published literature has shown that intrafraction motion of CTVB is minimal, with European institutes that use MR-linacs reducing PTV margins to 2–3 mm for the elective region [29]. However, literature is limited with regards to movement of the CTVA. Therefore, prior to the development of an MRgART SIB protocol, this unit investigated the motion of the CTVA of rectal cancer patients treated on MR-linacs with a view to reducing PTV margins. To understand the benefit of online MRgART, the motion of the CTVA was compared between a reference computed tomography (CT) planning scan and fractions on an MR-linac. The results of this work are presented here.

Materials and Methods

Patients and Treatment

Patients with locally advanced rectal cancer [AJCC TNM eighth edition stage T3 or greater and N0 or greater, circumferential margin ($\leq$1 mm from the tumour-free margin) involvement, extramural vascular invasion (direct invasion of blood vessel by tumour) positive, levators threatened) [30], suitable for nCRT and with no contraindications to MRI were eligible for treatment on the MR-linac (Elekta Unity, 1.5 T). Due to limitations in treatment beam field size, tumour size was restricted in a craniocaudal length of $<$12 cm. Staging investigations including CT and MRI, colonoscopy and biopsy were undertaken in local hospitals prior to referral to our unit. All patients' treatment pathways were discussed in central multidisciplinary meeting. Patients who consented to MR-linac treatment were recruited to an institution-approved study for treatment. Patients were treated with concurrent capecitabine 825 mg/m^2 BD or ralitrexed 3 mg/m^2 day 1 every 21 days in case of contraindication to or significant toxicity with capecitabine. A two-phase radiotherapy protocol was adopted: phase 1 – boost to the CTVA and involved nodes at 9 Gy/five fractions using daily recontouring and plan adaptation on MR-linac; followed by phase 2 – treatment to pelvic nodes and mesorectum using a C-arm linac at 45 Gy/25 fractions. Only phase 1 treatment fractions (five fractions treated on MR-linac) were included in this analysis.

Pre-treatment Planning

Patients treated on an MR-linac underwent a planning CT scan (Philips, Big Bore CT) and a MR scan, either on a diagnostic MRI (Siemens, Aera 1.5 T) or an MR-linac. The bladder filling protocol for a planning CT scan was to empty the bladder and drink 700 ml water 60 min before the scan; for MR-linac scans, the time interval prior to scanning was reduced to 45 min to simulate time spent on the bed during treatment. Scanning was carried out in the treatment position. Radiotherapy planning for phase 1 was carried out using the Monaco® v5.40.01 treatment planning system (Elekta AB, Stockholm, Sweden).

Image Acquisition during Treatment on the MR-linac

Imaging on the MR-linac included T2-weighted 2 min scans utilised for online adaptation, as described previously [25,31]. Imaging obtained at the start of treatment (pre-treatment image) and the end of treatment (post-treatment image) were used for analysis to determine intrafraction motion over the duration of treatment.

Intrafraction CTVA Motion Analysis

The GTV was contoured on pre-treatment and post-treatment imaging followed by a 10 mm isotropic expansion to create the CTVA and manually edited off bone as per unit protocol. The motion between pre-treatment CTVA and post-treatment CTVA was measured in Monaco® in six planes (anterior, posterior, right, left, superior and inferior), and at 10 mm intervals in the craniocaudal direction throughout the tumour. The median and interquartile range (IQR) as well as the mean and 95% confidence interval were calculated.

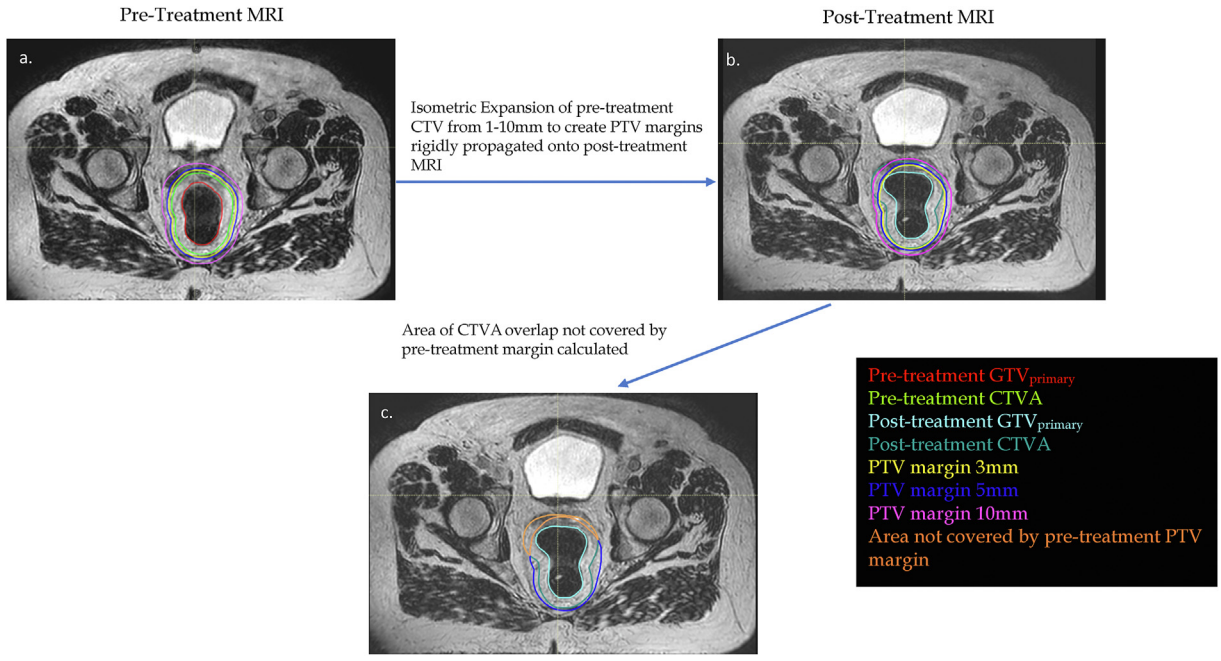

Fig 1. Workflow of the planning target volume (PTV) margin analysis. (a). Primary gross tumour volume ($GTV_{primary}$) contoured on pre-treatment magnetic resonance imaging (MRI) and expanded 10 mm to create the pre-treatment primary clinical target volume (CTVA) and edited off bone manually. 1–10 mm isotropic expansions of CTVA created. (b) $GTV_{primary}$ contoured on post-treatment MRI and expanded 10 mm to create post-treatment CTVA and edited off bone manually. PTV margins rigidly propagated to post-treatment MRI. (c) Example of area of overlap not covered by 5 mm pre-treatment PTV margins.

CTVA–PTV Margin Analysis

The methodology used for PTV analysis was similar to that described by Eijkelenkamp [29]. Pre-treatment CTVA was expanded isotropically by 1–10 mm to create PTV margins. PTV margins were rigidly propagated onto the post-treatment images, where the percentage overlap of post-treatment CTVA was calculated (Figure 1). The PTV margin was considered acceptable if the overlap of the CTVA was >95% in 90% of fractions [24]. Assessment of PTV margin overlapping 98% of post-treatment CTVA was also undertaken.

To understand the benefit of MRgART, the PTV analysis was repeated between the reference CT planning scan and MR-linac imaging where online manual recontouring and adaptation had not been carried out. The post-treatment MR is the closest match for comparison of MRgART and C-arm linac treatment with regards to treatment timing and replication of bladder filling, as well as representing the position of the tumour at the time the radiation beam was on. Isotropic expansions of CTVA from the reference CT were rigidly propagated to the post-treatment MR images using the pre-treatment MR/CT treatment registration determined by experienced MR-linac radiographers, prioritising the soft-tissue match of the GTV (Figure 2). The percentage overlap of the post-treatment CTVA was calculated as described above.

Results

Between January 2018 and December 2020, nine patients were recruited for nCRT on MR-linac. Each patient underwent five fractions on MR-linac during phase 1 treatment. Therefore, 45 fractions were analysed in total. The demographics of the included nine patients are shown in Table 1. The average timeframe between pre-treatment and post-treatment MRI was 39 min (range 30.34–59.19 min).

The median motion across all planes was 0 mm (Table 2). The largest range of motion was observed in the anterior rectal wall and right lateral wall due to bladder filling and gas distension, respectively. The median bladder filling between the pre-treatment and post-treatment scan was 160.6 cm^3 (IQR: 61.1–237.5 cm^3) in 31.42 min (IQR: 28.47–33.07 min). Patients with asymmetrical wall motion had tumour restricting movement of the lateral wall.

Analysis of MRgART determined that a rigidly propagated PTV margin of 3 mm overlapped with 95% of the post-treatment CTVA in 96% of fractions (Figure 3a). Increasing the threshold to cover 98% of post-treatment CTVA determined 91% of fractions would be acceptably covered with a 5 mm PTV margin (Figure 3b). Stratification of data by tumour position (see Table 2) showed that PTV margins in low and upper rectal tumours can be reduced further to a range of 2–4 mm to overlap with 95% and 98% of post-treatment CTVA, respectively. However, mid-rectal tumours showed greater motion and required a 4–8 mm PTV margin for the same overlap. The greatest motion of mid-rectal tumours was caused by gas filling within the rectum.

Using isotropically expanded PTV margins from the reference CT scan rigidly propagated to the post-treatment MRI without online manual recontouring and adaptation, analysis found that reducing PTV margins to 5 mm would only acceptably cover CTVA in 51% of fractions (Figure 4). It was also determined that only 76% of fractions acceptably covered CTVA using a 10 mm margin (Figure 4).

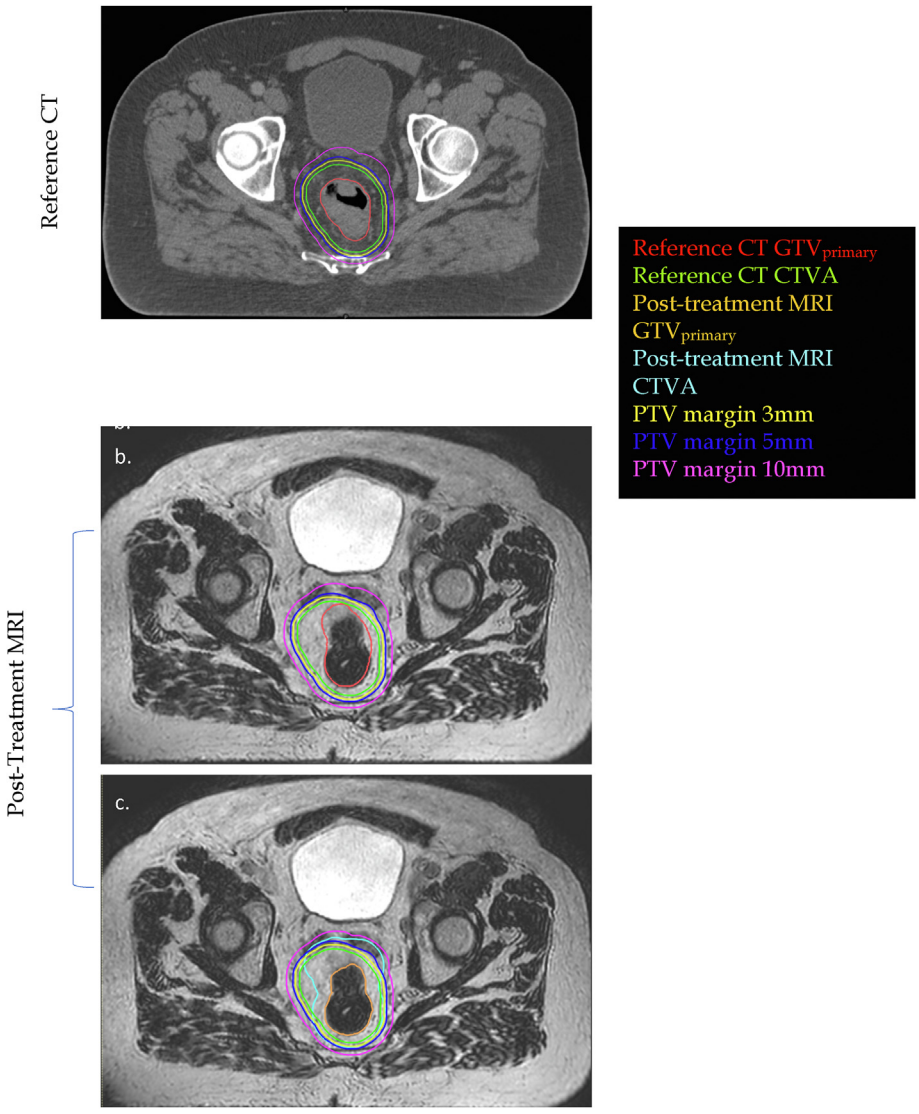

Fig 2. Workflow of non-adaptive planning target volume (PTV) margin analysis. (a) Primary gross tumour volume ($GTV_{primary}$) from the reference computed tomography (CT) expanded 10 mm to create the reference CT primary clinical target volume (CTVA) and edited off bone followed by 1–10 mm isotropic margins to create the PTV. (b) Reference CT contours rigidly propagated to post-treatment magnetic resonance imaging to demonstrate movement. (c) Position of post-treatment $GTV_{primary}$ and CTVA compared with reference CT scan PTV margins.

Discussion

The results of this study showed that intrafraction motion of CTVA in rectal cancer on MR-linac is usually minimal. More than 90% of fractions have overlap of 95% and 98% of post-treatment CTVA with a 3 mm and 5 mm PTV margin, respectively, giving confidence that geographical miss is unlikely. Therefore, reducing PTV margins to 3–5 mm on MR-linacs is safe and acceptable when performing daily manual recontouring, although caution would be required when treating mid-rectal tumours where movement is seen to be larger. Our results are similar to previously published literature conducted on MR-linac platforms [32,33].

In January 2021, the Royal College of Radiologists (RCR) published the 'National rectal cancer intensity-modulated radiotherapy guidelines' [34] recommending the reduction of PTV margins from 10 to 5 mm where online daily imaging can be carried out. Our results have shown a large interfraction motion between the reference CT and the treatment position of the PTV where manual recontouring was not used. When using a PTV margin of 10 mm as per previous convention [3,17], only 76% of fractions had adequate overlap with 95% of post-treatment CTVA. If reducing PTV margins to 5 mm, coverage of the PTV was acceptable for only 51% of fractions. Eijkelenkamp *et al.* [32] also determined that a 17 mm PTV margin was required to accommodate interfraction motion of rectal GTV. Although a true comparison is not possible between MR-linac treatment and C-arm linac, our results are similar to a recent study carried out by de Jong *et al.* [35] when conducting adaptive radiotherapy using cone-beam CT (CBCT); manual adjustment to 50% of fractions was required following set-up, and 55 of 60 fractions had V95% (volume of PTV receiving 95% of

Table 1
Patient and tumour characteristics. TNM staging performed using AJCC eighth edition; circumferential margin (CRM) involved: CRM ≤1 mm from the tumour-free margin; extramural vascular invasion (EMVI) present: direct invasion of blood vessel by tumour

		$n = 9$
Gender	Male	8 (89%)
	Female	1 (11%)
Age		62.56 years (range 37–74)
T stage	T3a	2 (22%)
	T3b	2 (22%)
	T3c	3 (33%)
	T4	2 (22%)
N stage	N0	2 (22%)
	N1	5 (56%)
	N2	2 (22%)
M stage	M0	7 (100%)
CRM involved	Yes	7 (78%)
	No	2 (22%)
EMVI present	Yes	7 (78%)
	No	2 (22%)
Tumour position	Low	3 (33%)
	Mid	3 (33%)
	Upper	3 (33%)

prescribed dose or more) less than required [35]. From this we determine that interfraction motion remains large in rectal cancer patients and MRgART provides a benefit in minimising this, especially when using an SIB protocol where matching is carried out to bone structures instead of the primary GTV.

However, within the new RCR guidelines [34], a new concept of 'internal clinical target volume (ICTV)' is introduced. The ICTV absorbs motion of the GTV without altering the position of the CTVA; essentially adding a 15 mm PTV margin from the GTV to cover both motion and microscopic disease. Based on this, treatment on CBCT with online daily imaging will be adequate to ensure no geographical miss of the target volume. Given that daily adaptive radiotherapy with manual online contouring mitigates against the effect of GTV motion, we would suggest that the CTV or ICTV component is removed from rectal radiotherapy treatment when using MRgART, and a 3–5 mm PTV margin added directly to the GTV. There is very little evidence in the literature with regards to the distribution of microscopic disease around the gross tumour [34] and in the proposed international consensus guidelines there is a move to remove the CTV component and apply a PTV margin directly to the GTV [24,33,36]. MRI is superior to CT imaging [27,37] and CBCT [38], with better visualisation of subclinical disease, such as nodes and extramural vascular invasion, which can be contoured as individual GTV regions of interest, to which a direct PTV margin can be applied. Removing the ICTV component in MRgART treatment will reduce the volume treated to a high dose, and allow for trials in dose escalation in order to improve the chances of achieving a cPR [39].

Currently, only 15–25% of patients achieve cPR on standard fractionation [15,17]. Dose-escalating rectal cancer treatment to doses >60 Gy has been shown to increase cPR response rates exponentially [40]. Achieving cPR is known to improve survival outcomes; Habr-Gama *et al.* [41] observed that patients who achieved cPR after nCRT showed overall survival and disease-free survival rates of 100% and 92%, respectively, at 5 years and that in these patients who achieved cPR, surgery can be deferred until the first signs of recurrence [41].

However, not all attempts at dose escalation have succeeded in increasing cPR rates. Couwenberg *et al.* [36] showed an improved 'near complete response' rate in the dose-escalated cohort without improvement in the cPR rates. One hypothesis is that the PTV boost was limited by proximity of OARs with a minimum PTV boost dose of 58.9 Gy compared with the aim of achieving 65 Gy [36]. Second, adaptation was not used and therefore interfraction motion was not mitigated against. As such, despite the lower boost dose, patients experienced greater gastrointestinal toxicity in the boost cohort than in the control arm, especially at 3 months post-treatment, with two patients reporting grade 4 toxicity [36]. Concerns over toxicity also limit recruitment to dose-escalated trials [42]. Using MRgART dose to OARs can be optimised to ensure toxicity is limited to enable safer dose escalation.

The limitation of our study is the small number of patients, which may not be representative of the patient population, but our results are in keeping with similar studies carried out in other institutions [25,32,35]. Therefore, we believe that we can implement a direct GTV–PTV margin within our workflow. Further work will be

Table 2
Median and mean motion between the pre-treatment primary clinical target volume (CTVA) and the post-treatment CTVA

	Median (mm)	Interquartile range (mm)	Mean (mm)	95% confidence interval
Anterior	0	−3 to 1	−1.59	−2.05 to 1.14
Posterior	0	0 to 2	0.04	−0.27 to 0.35
Left	0	−1 to 2	0.43	0.13 to 0.73
Right	0	−2 to 2	0.01	−0.36 to 0.37
Superior	0	0 to 2	1.13	0.55 to 1.72
Inferior	0	−2 to 0	−1.20	−2.33 to 0.66

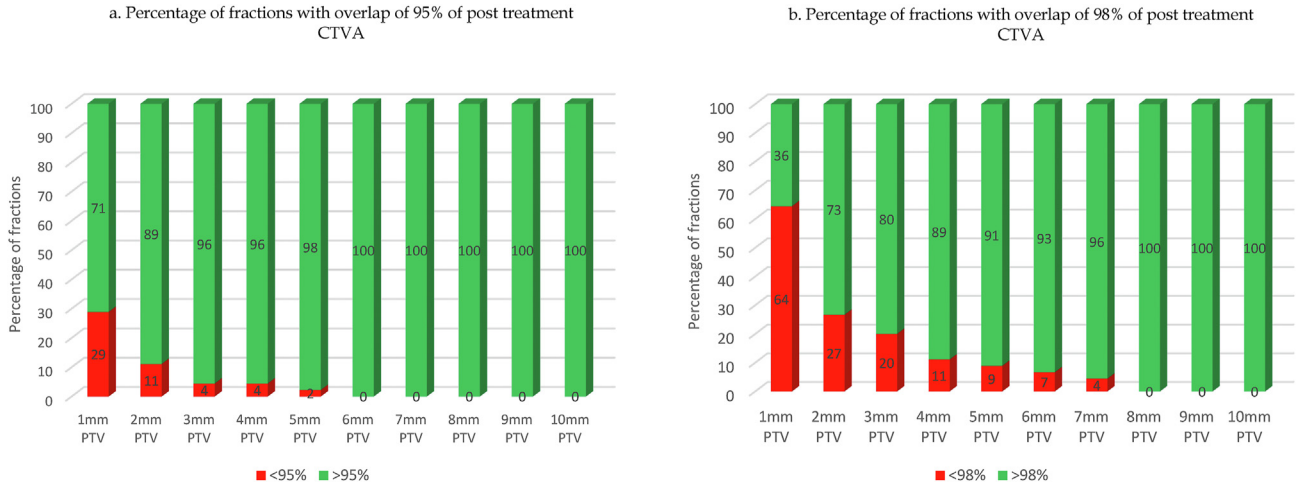

Fig 3. Bar chart showing the percentage of fractions with overlap of the post-treatment primary clinical target volume (CTVA) with the pre-treatment planning target volume (PTV) margins in all rectal tumours.

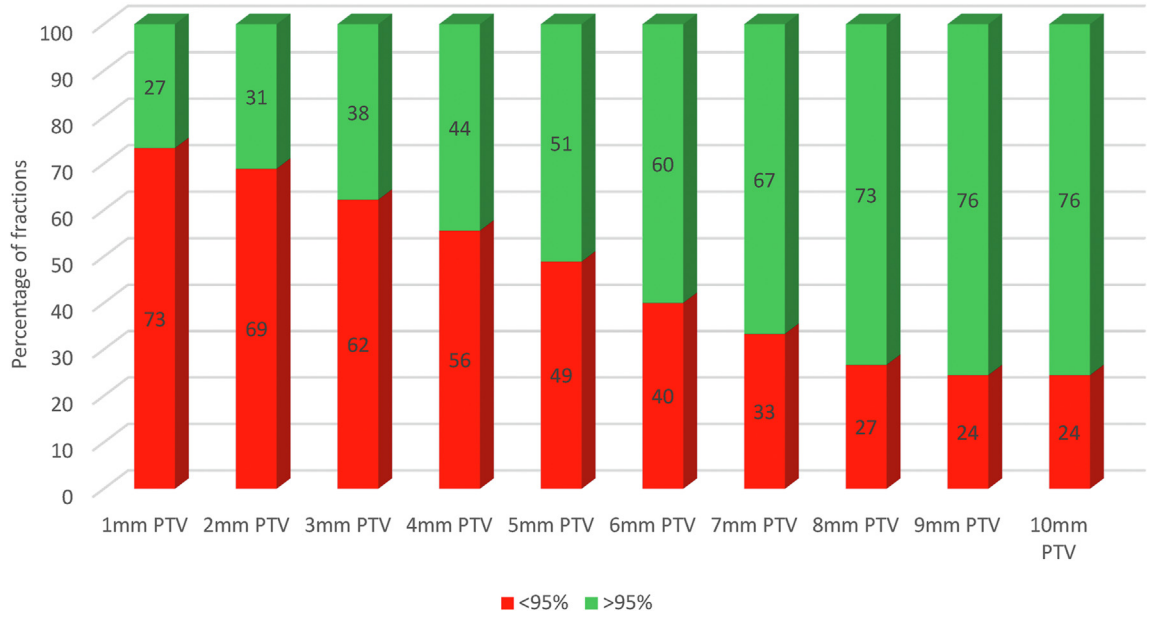

Fig 4. Non-adaptive radiotherapy environment: bar chart showing the percentage of fractions with overlap of 95% of the post-treatment primary clinical target volume (CTVA) with the pre-treatment planning target volume (PTV) margins from the reference computed tomography scan.

required to validate this in an independent cohort. Another limitation is that the comparison of MRgART and non-adaptive image-guided radiotherapy is not a true representation of treatment on a C-arm linac. First, treatment on a C-arm linac is shorter than on an MR-linac and thus intrafraction motion may be less on a C-arm linac. Second, registration of the reference CT scan with a pre-treatment MR image might represent a worst-case scenario of geographical miss based on a snapshot of the position of the target, thus excluding intrafraction motion during treatment. However, based on the findings of this study, we conclude that intrafraction motion of the CTVA is minimal, even for treatment >40 min and is, therefore, unlikely to impact on the results presented here.

Conclusion

PTV margins can be safely reduced to 3–5 mm when treating rectal cancer patients on an MR-linac and adequately cover post-treatment CTVA when delivering MRgART mitigating against interfraction motion. These results have helped our unit develop a SIB protocol for use on MR-linacs, which is designed to benefit all patients with rectal cancer without increasing departmental workload. As the UK implements new RCR guidelines [34] in the treatment of rectal cancer, we believe that using MRgART can remove the need for the ICTV component and apply a direct margin to the GTV to generate a PTV. This opens the

possibility of designing trials of radiation dose escalation in rectal cancer on MR-linacs in order to improve cPR rates, while ensuring limited toxicity to patients.

Author contributions

SB is the guarantor of integrity of the entire study. MI, AD, JC and AM were responsible for study concepts and design. MI carried out the literature research, experimental studies/data analysis and the statistical analysis. MI, AD and SB prepared the manuscript. All authors edited the manuscript.

Conflicts of interest

The Royal Marsden Hospital and The Institute of Cancer Research are members of the Elekta MR-Linac Consortium, which aims to coordinate international collaborative research relating to the Elekta Unity (MR-Linac). Elekta (Elekta AB, Stockholm, Sweden) and Philips (Philips, Best, Netherlands) are commercial members of the MR-Linac Consortium. Elekta financially supports consortium member institutions with research funding, education and travel costs for consortium meetings. No commercial financial support was received from any organisation for the submitted work.

Acknowledgements

This study represents independent research supported by the National Institute for Health Research Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. This work was supported by The Institute of Cancer Research and Cancer Research UK (CRUK) grant number C33589/A28284 and the Royal Marsden Cancer Charity.

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