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Original Research Article

Investigation of changes in planning target volume and regression probability of rectal boost using in-silico cone-beam computed tomography-guided online-adaptive radiotherapy

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ABSTRACT

Background and purpose: Radiotherapy boost to the primary tumour may enable organ preservation in locally advanced rectal cancer (LARC). This study evaluated cone-beam computed tomography (CBCT)-guided online-adaptive radiotherapy (ART) to reduce rectal boost planning target volume (PTV_{Boost}) margins and allow dose escalation.

Materials and methods: Eleven LARC patients were included in this *in silico* study. Population-based PTV_{Boost} margins were computed for non-adaptive and online-ART using van Herk's formalism. Dose/volume results were compared between: non-adaptive RT with a 25 x 2.16 Gy boost ($Non\text{-}ART_{54Gy}$), ART with a 25 x 2.16 Gy boost (ART_{54Gy}), and ART with an escalated boost of 25 x 2.4 Gy (ART_{60Gy}). Tumour regression probability was compared between each plan using a dose–response model.

Results: PTV_{Boost} margins for non-adaptive vs. online-ART were 14.2 vs. 3.3 mm in the antero-posterior, 5.0 vs. 3.2 mm in the left–right, and 12.3 vs. 8.7 mm in the supero-inferior axes. PTV_{Boost} and pelvic lymph node PTV coverage (V95%) were significantly improved with ART_{54Gy} and ART_{60Gy} compared to $Non\text{-}ART_{54Gy}$ ($p < 0.001$). High-priority organ-at-risk constraints (priority 1&2) were violated in 26.8 % of cases for $Non\text{-}ART_{54Gy}$, 21.2 % of cases for ART_{54Gy}, and 20.8 % of cases for ART_{60Gy}. Tumour regression probability was superior for ART_{60Gy} (20.8 %) compared to ART_{54Gy} (17.0 %, $p < 0.001$) and $Non\text{-}ART_{54Gy}$ (16.9 %, $p < 0.001$).

Conclusions: Online-ART significantly reduce rectal boost PTV margin. It allows better target volume coverage with a similar risk of radiation-induced toxicities, even when escalating the dose. Therefore, online-ART should be considered to perform dose-escalation in LARC patients with the objective of organ preservation.

1. Introduction

Rectal cancer represents about 30 % of all colorectal cancer. For locally advanced rectal cancer (LARC), current management combines radiotherapy (RT), chemotherapy, and surgery [1,2]. RT and chemotherapy can be given concomitantly during a long-course radiochemotherapy as part of total neoadjuvant therapy [2–6]. More recently, TNT combined with induction or consolidation chemotherapy can also be used as a potential definitive treatment under a "watch and wait" strategy for organ preservation [6,7]. To improve clinical complete response rates, a RT boost to the primary tumour can be advised, either using external beam (EB)RT or contact x-ray brachytherapy [6,8–13]. Contact x-ray brachytherapy has shown promising organ preservation rates in early stages, but data for LARC remain scarce [12,13]. Using EBRT, clinical complete response rate can reach nearly 50 % [6]. However, dose escalation to the primary tumour is controversial due to potential excessive toxicities [14]. Unlike contact x-ray brachytherapy, EBRT must integrate the tumour interfraction motion in the boost planning target volume (PTV_{Boost}), increasing the total irradiated volume [15–19]. This limits the opportunity for EBRT dose escalation, which would potentially increase the complete response rate [3,20].

Recent technical innovations could be used for dose-escalation of the primary rectal tumour. Among them, cone-beam computed tomography (CBCT)-guided online-adaptive RT (ART) is an emerging technology

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enabling daily delineation of organs-at-risk (OARs) and target volumes, with daily planning in an acceptable time for clinical application [21,22]. This technique is already used in neoadjuvant rectal cancer treatment [23]. By eliminating the interfraction motion impact, CBCT-guided online-ART can potentially reduce the PTV margins and allow dose-escalation compared to non-adaptive strategies.

The first objective of this *in-silico* study was to compute population-based PTV margins for rectal boost EBRT. We determined the PTV margin that should be applied in non-adaptive and in CBCT-guided online-ART strategies to assess whether online-ART allowed a PTV reduction. The second objective was to perform a dose-volume analysis evaluating if CBCT-guided online-ART allows primary tumour dose escalation while preserving pelvic OARs.

2. Materials and methods

2.1. Patients

From January to October 2023, we prospectively included 11 patients treated by RT for rectal tumour in our hospital. Children and patients with prior pelvic RT were excluded. No other inclusion or exclusion criteria applied. This study followed the Declaration of Helsinki and was approved by the ethics committee of the Cliniques universitaires Saint-Luc (reference number: B4032022000061 – July 22, 2022). All participants provided written informed consent.

2.2. Treatment

A 3-mm-slice-thickness planning-CT (Aquilion LB, Toshiba Medical Systems, Tokyo, Japan) was acquired with intravenous iodine contrast (120 kVp, 400 mAs). The planning-CT and RT sessions were performed supine, with a comfortably full bladder (300 mL water, 30 min prior), without rectum preparation. The RT planning was done on the RayStation Planning system (clinical versions 9B and 12A, RaySearch Laboratories, Stockholm, Sweden). The boost gross tumour volume (GTV_{boost}) was the primary tumour delineated on the planning CT, adapted according to clinical examination, rectoscopy, and a rigid co-registration with T2-weighted magnetic resonance imaging (MRI, 3.5 mm slices, Ingenia 3T, Philips Healthcare, Amsterdam, The Netherlands or SIGNA Premier 3T, GE Healthcare, Boston, MA, USA). The clinical boost target volume (CTV_{boost}) included the GTV_{boost} and the circumferential rectal wall at each transversal CT slice where the tumour was present. The elective CTV encompassed lymph node areas according to international recommendations [24]. The RT was delivered by two linear accelerators (Halcyon® and Ethos®, Varian a Siemens Healthineers Company, Palo Alto, Calif., USA). Although Ethos® is dedicated to online-ART only its non-adaptive mode was used in this study. Daily CBCT using the "pelvis fast" or "pelvis large fast" modes (acquisition time: 21.2 and 25 s, respectively) was acquired for image-guided RT. Two supplementary CBCTs were obtained during the first five RT sessions (short-course or long-course RT) and weekly thereafter (long-course RT) to evaluate the intrafraction motion of pelvic organs and target volumes.

2.3. Boost planning target volume definition

The PTV_{Boost} was defined using the van Herk's formalism [25]. Systematic and random geometrical treatment errors were integrated in a quadratic sum to derive the PTV_{Boost} margin:

$$PTV_{Boost} = \alpha\Sigma + \beta\sigma - \beta\sigma_p \quad (1)$$

With Σ and σ as standard deviations of systemic and random errors, respectively, σ_p as the penumbra width, and $\alpha = 2.5$, $\beta = 1.64$ ensuring 90 % of patients receive 95 % of the dose [25]. For non-adaptive RT, PTV_{Boost} margin ($PTV_{Non\text{-}ART}$) included the systematic errors related to tumour motion (Σ_{TM}), setup (Σ_{SETUP}), and delineation variability (Σ_D); and random errors related to tumour motion (σ_{TM}), setup (σ_{SETUP}), and penumbra (σ_p) [18,25].

$$PTV_{Non-ART} = \alpha\sqrt{\Sigma_{TM}^2 + \Sigma_{SETUP}^2 + \Sigma_D^2} + \beta\sqrt{\sigma_{TM}^2 + \sigma_{SETUP}^2 + \sigma_p^2} - \beta\sigma_p \quad (2)$$

While this formula applied to spherical, rigid tumour with tumour motion described by translation only, this was not applicable for the rectum [18,25]. In this study, the CTV_{boost} is rectal segment, whose motion could be divided into translational (*TMT*) and deformation (*TMD*) components. Both TMT and TMD values approached a Gaussian distribution, for which a systematic and random error can be computed and added:

$$\begin{aligned} PTV_{Non-ART} = {} & \alpha\sqrt{\Sigma_{TMT}^2 + \Sigma_{TMD}^2 + \Sigma_{SETUP}^2 + \Sigma_D^2} \\ & + \beta\sqrt{\sigma_{TMT}^2 + \sigma_{TMD}^2 + \sigma_{SETUP}^2 + \sigma_p^2} - \beta\sigma_p \end{aligned} \quad (3)$$

For online-ART PTV_{Boost} margin (PTV_{ART}) computation, the daily delineation of organ-at-risks and target volumes, along with the computation of a new plan for each session, eliminated patient setup variations (Σ_{SETUP} and σ_{SETUP}). However, as a result of the daily CTV_{boost} adjustments, we should incorporate a random component of the delineation variability error (σ_D). Finally, since interfraction motion is compensated by online-ART, this interfraction motion *(ITM)* should be integrated in the non-adaptive margin, while when using daily online-ART, only the intrafraction motion (*iTM*) should be considered, which is minimal compared to interfraction motion [26]. Therefore, it has been assumed that integrating interfraction motion uncertainties in the PTV would also compensate for intrafraction motion in the non-adaptive strategy. By integrating all these errors, the formula for the non-adaptive PTV margin becomes:

$$\begin{aligned} PTV_{Non-ART} = {} & \alpha\sqrt{\Sigma_{ITMT}^2 + \Sigma_{ITMD}^2 + \Sigma_{SETUP}^2 + \Sigma_D^2} \\ & + \beta\sqrt{\sigma_{ITMT}^2 + \sigma_{ITMD}^2 + \sigma_{SETUP}^2 + \sigma_p^2} - \beta\sigma_p \end{aligned} \quad (4)$$

And for the online-ART PTV margin:

$$PTV_{ART} = \alpha\sqrt{\Sigma_{iTMT}^2 + \Sigma_{iTMD}^2 + \Sigma_D^2} + \beta\sqrt{\sigma_{iTMT}^2 + \sigma_{iTMD}^2 + \sigma_D^2 + \sigma_p^2} - \beta\sigma_p \quad (5)$$

All errors and margins were computed in the three dimensions, reflecting different rectal motion patterns along these axis [17,18,27–29] (See Supplementary Methods for computation of these errors).

2.4. Plan evaluation

Three different plans were generated and virtually delivered using an emulator of the Ethos' adaptive treatment planning system: (1) a Non-adaptive plan using $PTV_{Non\text{-}ART}$ with a boost dose of 2.16 Gy per fraction ($Non\text{-}ART_{54Gy}$),(2) an adaptive plan using PTV_{ART} with a boost dose of 2.16 Gy per fraction (ART_{54Gy}), and (3) an adaptive plan using PTV_{ART} with a boost dose of 2.4 Gy per fraction (ART_{60Gy}). This emulator simulates the different adaptive radiotherapy steps: after the CBCT import from a database, the software performs an artificial intelligence-based delineation of some OARs called 'influencers' (in this study: the rectum, bladder, and bowel), which are reviewed and manually edited if inaccurate by a radiation oncologist. Then, target volumes are automatically propagated using a structure-guided deformable registration between planning CT and daily CBCT, which is driven by the influencer volumes. These target volumes are also evaluated and adjusted if needed, using the planning CT and MRI displayed on another screen. Finally, an adaptive plan is computed and compared with the non-adaptive initial plan, with the best option selected by a radiation oncologist. Aside from replacing the imported CBCT by real-time

Table 1
Dose/volume objectives classed according to the priority for plan generation. The small bowel is defined as bowel loops, genitalia encompass external genital organs (vulva in women; penis and testicles in men). *L: Left, R: Right.*

Dose/volume objectives for the whole treatment	Dose/volume objectives per session	Priority
PTV Boost V95% > 98 %	PTV Boost $V_{95\%}$ > 98 %	1
PTV Boost V105% < 2 %	PTV Boost $V_{105\%}$ < 2 %	
PTV Low V95% > 98 %	PTV Low $V_{95\%}$ > 98 %	
Small Bowel D0.1 cm^3 < 50 Gy	Small Bowel $D^3_{0.1\ cm}$ < 2 Gy	
Small Bowel V15 Gy < 200 cc	Small Bowel $V_{0.6\ Gy}$ < 200 cc	2
Small Bowel V45 Gy < 65 cc	Small Bowel $V_{1.8\ Gy}$ < 65 cc	
Colon&Sigmoid D0.1 cm^3 < 54 Gy	Colon&Sigmoid $D^3_{0.1cm}$ < 2.16 Gy	
Bladder D35% < 40 Gy	Bladder $D_{35\%}$ < 1.6 Gy	
Bladder D5% < 50 Gy	Bladder $D_{5\%}$ < 2 Gy	
Bladder D50% < 35 Gy	Bladder $D_{50\%}$ < 1.4 Gy	
Femoral joint L/R D35% < 40 Gy	Femoral joint L/R $D_{35\%}$ < 1.6 Gy	3
Femoral joint L/R D5% < 50 Gy	Femoral joint L/R $D_{5\%}$ < 2 Gy	
Femoral joint L/R D50% < 30 Gy	Femoral joint L/R $D_{50\%}$ < 1.2 Gy	
Genitalia D35% < 30 Gy	Genitalia $D_{35\%}$ < 1.2 Gy	
Genitalia D5% < 40 Gy	Genitalia $D_{5\%}$ < 1.6 Gy	
Genitalia D50% < 20 Gy	Genitalia $D_{50\%}$ < 0.8 Gy	

acquisition, all these steps are identical to clinical procedures. For Non-ART_{54Gy}, the non-adaptive plan was always chosen; for ART_{54Gy} and ART_{60Gy}, the adaptive plan was systematically selected. For the purpose of this study, only the primary rectal tumour was boosted, without considering lymph nodes dose escalation. Patients with metastatic disease received radical radiotherapy for the pelvic tumour and lymph nodes, metastasis treatments were handled independently.

For all plans, 1.8 Gy per fraction was prescribed to the elective PTV (PTV_{Low}), corresponding to a conventional dose of 45 Gy to pelvic lymph nodes based on international recommendations [2,24]. Target volume goals and organ-at-risk dose constraints were classified according to their priority (from 1 = most important to 3 = least important, Table 1).

Non-ART_{54Gy}, ART_{54Gy}, and ART_{60Gy} plans were obtained for 33 virtual RT sessions (3 per patient) and compared according to their compliance with dose/volume objectives.

2.5. Tumour regression probability evaluation

The tumour regression probability (TRP) was compared between Non-ART_{54Gy}, ART_{54Gy}, and ART_{60Gy} plans. The per-voxel CTV_{boost} dose (*Dvoxel*) was introduced in the model developed by Applet et al., 2013 [20]. Briefly, this model integrated the *Dvoxel*, the tumour volume (*Tvol*, in cm^3) and the *N-stage* to calculate TRP:

$$TRP_{voxel} = \frac{e^{-2.634 + 0.0349Dvoxel - 0.0058Tvol - 0.6252Nstage}}{1 + e^{-2.634 + 0.0349Dvoxel - 0.0058Tvol - 0.6252Nstage}} \quad (6)$$

Coefficients were fixed to evaluate a TRP for a Tumour regression grade (TRG) 1, corresponding to complete response without any residual tumour cell, for an actual delivered dose [20,30]. N-stage and tumour volume were reported for each patient. For each individual fraction, TRP was calculated as the average of all TRP_{voxel} values within the CTV_{boost}.

2.6. Data analysis

Median values with interquartile range were reported and compared using the Wilcoxon signed-rank test. Statistical comparisons between plans were performed using a linear mixed model, with the patient as a random factor due to multiple observations per patient. Post-hoc

Table 2
Characteristics of the patients. CBCT: Cone-beam computed tomography, SD: Standard deviation.

	Rectum RT patients
N	11
Gender	
Male	10
Female	1
Age (mean +/- SD)	57.6 +/- 15.0
Tumour location	
Low rectum	3
Middle rectum	5
High rectum	3
T stage	
T3	8
T4	3
N stage	
N0	1
N1	3
N2	7
M stage	
M0	8
M1	3
Number CBCTs for interfraction motion analysis	95
Number CBCTs for intrafraction motion analysis	285

Table 3
Systematic (Σ) and random (σ) error values in mm for the tumour motion, delineation variability, and setup that are integrated in the total PTV margin. ART: Adaptive radiotherapy, PTV: Planning target volume.

	Antero-posterior	Left-right	Supero-inferior
	Tumour motion translation (*TMT*)		
Interfraction (*ITMT*)			
Σ	4.2	1.1	2.5
σ	3.6	1.4	3.4
Intrafraction (*iTMT*)			
Σ	0.6	0.3	0.7
σ	1.5	0.8	1.6
	Tumour motion deformation (*TMD*)		
Interfraction (*ITMD*)			
Σ	1.1	0.5	1.0
σ	0.6	0.4	1.4
Intrafraction (*iTMD*)			
Σ	0.6	0.3	0.6
σ	0.4	0.2	1.7
	Delineation (*D*)		
Σ	0.6	1.1	2.5
σ	0.4	0.4	1.9
	Setup		
Σ	0.5	0.5	0.5
σ	1.0	1.0	1.0
	Penumbra (*p*)		
	2.9	2.9	2.9
	PTV margins		
$PTV_{Non-ART}$	14.2	5.0	12.3
PTV_{ART}	3.3	3.2	8.7

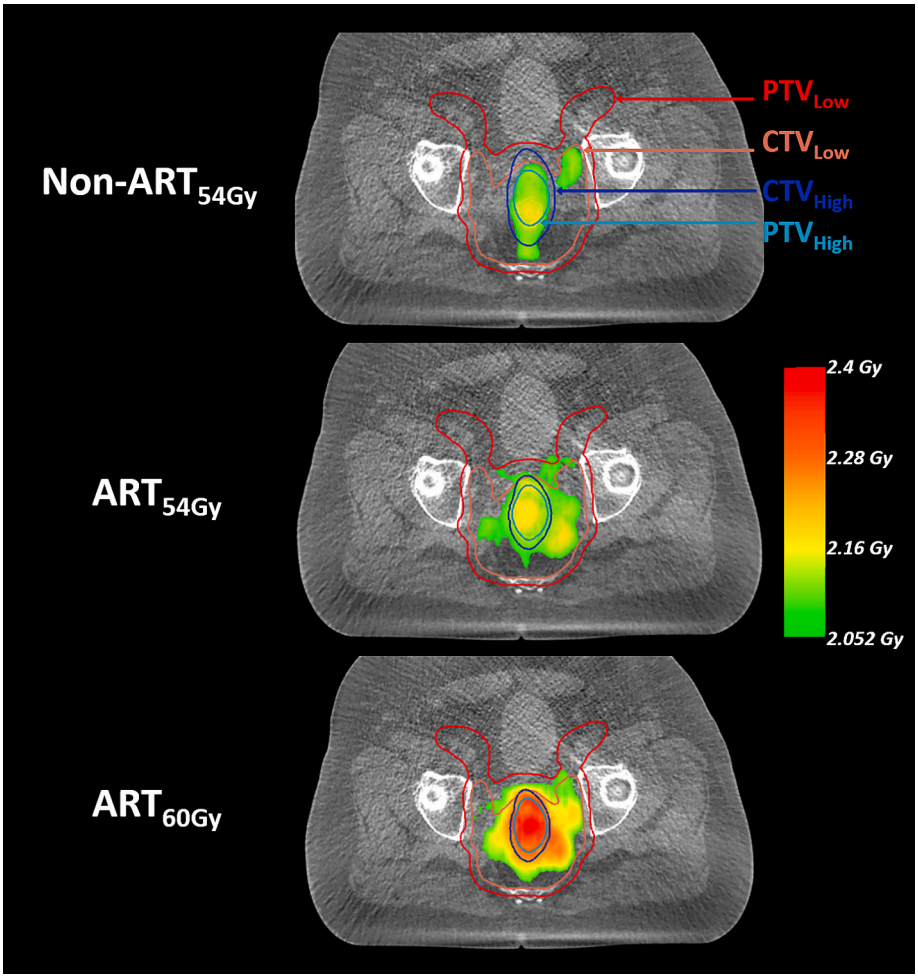

Fig. 1. Comparison between $PTV_{Non\text{-}ART}$ and PTV_{ART} volume and dose distribution of Non-ART_{54Gy}, ART_{54Gy}, and ART_{60Gy}. The dark blue and dark red lines are the PTV_{Boost} and the PTV_{Low}, respectively. The light blue and light red lines are the CTV_{Boost} and the CTV_{Low}, respectively. $PTV_{Non\text{-}ART}$ was used only for Non-ART_{54Gy} plans and is significantly bigger ($p < 0.0001$) than the PTV_{ART} used for ART_{54Gy} and ART_{60Gy} plans. The isodose levels 2.052 Gy and 2.16 Gy correspond to 95 % and 100 % respectively of the prescribed dose to the primary tumour in plans Non-ART_{54Gy}, and ART_{54Gy}. The isodose levels 2.28 Gy and 2.4 Gy correspond to 95 % and 100 % respectively of the prescribed dose to the primary tumour in plan ART_{60Gy}. Coverage of the PTV_{Boost} by the 95 % isodose is achieved with ART_{54Gy}, or ART_{60Gy}, but not with Non-ART_{54Gy}. ART: Adaptive radiotherapy, CTV: Clinical target volume, PTV: Planning target volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pairwise comparisons between plans were performed and adjusted for multiple comparisons using the Benjamini-Hochberg method. A p-value < 0.05 was considered significant. Image analyses for error quantifications and TRP calculation were performed using in-house developed Python (version 3.10) scripts on Visual Studio Code (version 1.18.1). All statistical analyses were performed on RStudio (R version 4.2.1) using the "tidyverse" package.

3. Results

Demographic characteristics of the 11 included patients are reported in Table 2.

Setup systematic and random error values were set to 0.5 and 1 mm, respectively, in all directions according to Nijkamp et al., 2009 [18]. The penumbra was fixed at 2.9 mm [31]. Tumour motion errors, delineation errors, and final PTV margins for non-adaptive and online-ART strategies are reported in Table 3.

The median $PTV_{Non\text{-}ART}$ volume was 214.3 cm^3 (188.1 cm^3–341.8 cm^3), significantly larger than the median PTV_{ART} volume of 122.5 cm^3 (108.3 cm^3–209.8 cm^3; $p < 0.001$, Wilcoxon paired; Fig. 1).

Among the 33 fractions delivered for each plan, the most frequently violated dose/volume goal was the small bowel volume receiving over 15 Gy (priority 2), for the ART_{54Gy} and the ART_{60Gy} plans (n = 20/33 and 19/33, respectively). For the Non-ART_{54Gy}, the most frequent violation was the PTV_{Boost} volume receiving more than 95 % of the prescribed dose (priority 1). Median PTV_{Boost} and PTV_{Low} volumes covered by at least 95 % of the prescribed dose were significantly lower with Non-ART_{54Gy} plan compared to ART_{54Gy} and ART_{60Gy} ($p < 0.001$ in each case). There were 70/132, 20/132, and 18/132 priority 1 dose/volume objective violations for Non-ART_{54Gy}, ART_{54Gy}, and ART_{60Gy} plans, respectively. Violations occurred for 45/198 priority 2 dose/volume objectives in Non-ART_{54Gy} plans, 33/198 in ART_{54Gy} plans, and 34/198 in ART_{60Gy} plans (Table 4).

The median TRP value was 16.9 % [12.6 %–19.0 %] for Non-ART_{54Gy}, 17.0 % [12.7 %–19.1 %] for ART_{54Gy}, and 20.8 % [15.7 %–23.3 %] for ART_{60Gy}. These values were significantly higher for ART_{60Gy} compared to the two other plans (linear mixed effect model, $p < 0.001$), but not significantly different between Non-ART_{54Gy} and ART_{54Gy} ($p = 0.16$; Fig. 2).

4. Discussion

In this study, we proposed a population-based PTV definition for both non-adaptive and CBCT-guided online-adaptive RT (ART)

Table 4
Dose/volume results of the 33 RT sessions delivered. Comparisons between values of each plan were performed using a linear mixed effect model with post-hoc analysis and correction for multiple comparisons using the Benjamini-Hochberg method.

Dose/volume objectives per RT session	Priority	Non-ART$_{54Gy}$		ART$_{54Gy}$			ART$_{60Gy}$			
		N violations	Median value [IQR]	N violations	Median value [IQR]	Comparison with Non-ART$_{54Gy}$	N violations	Median value [IQR]	Comparison with Non-ART$_{54Gy}$	Comparison with ART$_{54Gy}$
PTV Boost $V_{95\%} >$ 98 %	**1**	*29*	93.3 % [81.4 %–97.3 %]	*4*	98.9 % [98.6 %–99.4 %]	****	*4*	98.9 % [98.6 %–99.0 %]	****	ns
PTV Boost $V_{105\%} <$ 2 %		*7*	0.0 % [0.0 %–1.1 %]	*0*	0.0 % [0.0 %–0.0 %]	ns	*0*	0.0 % [0.0 %–0.0 %]	ns	ns
PTV Low $V_{95\%} >$ 98 %		*17*	98.0 % [96.2 %–98.9 %]	*0*	99.8 % [99.8 %–99.9 %]	****	*0*	99.9 % [99.8 %–99.9 %]	****	ns
Small Bowel $D_{0.1\ cm^3} <$ 2 Gy		*17*	2.01 Gy [1.95 Gy–2.21 Gy]	*16*	1.99 Gy [1.90 Gy–2.17 Gy]	ns	*14*	1.97 Gy [1.92 Gy–2.21 Gy]	ns	ns
Small_Bowel $V_{0.6\ Gy} <$ 200 cc	**2**	*20*	240 cm^3[141 cm^3- 459 cm^3]	*20*	222 cm^3[169 cm^3– 347 cm^3]	ns	*19*	222 cm^3[173 cm^3– 360 cm^3]	ns	ns
Small_Bowel $V_{1.8\ Gy} <$ 65 cc		*7*	26.3 cm^3[6.2 cm^3- 45.2 cm^3]	*6*	14.0 cm^3[4.2 cm^3- 43.3 cm^3]	ns	*6*	15.4 cm^3[6.6 cm^3- 41.8 cm^3]	ns	ns
Colon&Sigmoid $D^3_{0.1\ cm} <$ 2.16 Gy		*5*	1.78 Gy [0.70 Gy–2.10 Gy]	*6*	1.85 Gy [82 Gy–2.14 Gy]	ns	*6*	1.83 Gy [0.80 Gy–2.05 Gy]	*	ns
Bladder $D_{35\%} <$ 1.6 Gy		*3*	1.25 Gy [1.10 Gy–1.36 Gy]	*0*	1.09 Gy [0.85 Gy–1.29 Gy]	ns	*1*	1.24 Gy [0.94 Gy–1.42 Gy]	ns	ns
Bladder $D_{5\%} <$ 2 Gy		*8*	1.81 Gy [1.57 Gy–1.98 Gy]	*1*	1.78 Gy [1.70 Gy–1.89 Gy]	ns	*2*	1.81 Gy [1.75 Gy–1.86 Gy]	ns	ns
Bladder $D_{50\%} <$ 1.4 Gy		*2*	1.07 Gy [0.96 Gy–1.21 Gy]	*0*	0.80 Gy [0.67 Gy–1.13 Gy]	**	*0*	1.09 Gy [0.80 Gy–1.25 Gy]	ns	**
Femoral joint Left $D_{35\%} <$ 1.6 Gy	**3**	*0*	0.61 Gy [0.55 Gy–0.71 Gy]	*0*	0.66 Gy [0.54 Gy–0.69 Gy]	ns	*0*	0.67 Gy [0.62 Gy−0.74 Gy]	*	*
Femoral joint Right $D_{35\%} <$ 1.6 Gy		*0*	0.63 Gy [0.55 Gy–0.67 Gy]	*0*	0.59 Gy [0.49 Gy−0.67 Gy]	ns	*0*	0.65 Gy [0.61 Gy−0.70 Gy]	ns	*
Femoral joint Left $D_{5\%} <$ 2 Gy		*0*	1.06 Gy [0.95 Gy–1.11 Gy]	*0*	1.01 Gy [0.92 Gy–1.08 Gy]	ns	*0*	1.06 Gy [0.95 Gy–1.12 Gy]	ns	ns
Femoral joint Right $D_{5\%} <$ 2 Gy		*0*	1.07 Gy [0.88 Gy–1.11 Gy]	*0*	0.96 Gy [0.90 Gy–1.06 Gy]	ns	*0*	1.03 Gy [0.94 Gy–1.08 Gy]	ns	ns
Femoral joint Left $D_{50\%} <$ 1.2 Gy		*0*	0.52 Gy [0.31 Gy–0.57 Gy]	*0*	0.49 Gy [0.43 Gy−0.55 Gy]	ns	*0*	0.52 Gy [0.42 Gy−0.56 Gy]	ns	ns
Femoral joint Right $D_{50\%} <$ 1.2 Gy		*0*	0.47 Gy [0.27 Gy−0.57 cGy]	*0*	0.44 Gy [0.33 Gy−0.50 Gy]	ns	*0*	0.43 Gy [0.34 Gy–0.50 Gy]	ns	ns
Genitalia $D_{35\%} <$ 1.2 Gy		*0*	0.14 Gy [0.11 Gy–0.21 Gy]	*0*	0.11 Gy [0.9 Gy−0.19 Gy]	ns	*0*	0.13 Gy [0.09 Gy−0.20 Gy]	ns	ns
Genitalia $D_{5\%} <$ 1.6 Gy		*1*	0.49 Gy [0.30 Gy−0.56 Gy]	*0*	0.48 Gy [0.25 Gy−0.53 Gy]	ns	*0*	0.39 Gy [0.30 Gy−0.64 Gy]	ns	ns
Genitalia $D_{50\%} <$ 0.8 Gy		*0*	0.08 Gy [0.08	*0*	0.08 Gy [0.07	ns	*0*	0.08 Gy [0.06	ns	ns

(*continued on next page*)

Table 4 (*continued*)

Dose/volume objectives per RT session	Priority	Non-ART$_{54Gy}$		ART$_{54Gy}$			ART$_{60Gy}$			
		N violations	Median value [IQR]	N violations	Median value [IQR]	Comparison with Non-ART$_{54Gy}$	N violations	Median value [IQR]	Comparison with Non-ART$_{54Gy}$	Comparison with ART$_{54Gy}$
			Gy−0.16 Gy]		Gy−0.11 Gy]			Gy−0.15 Gy]		

*ns: Not significant, * p-value < 0.05, ** p-value < 0.01, **** p-value < 0.001.*
(A)RT: (Adaptive) radiotherapy, IQR: Interquartile range.

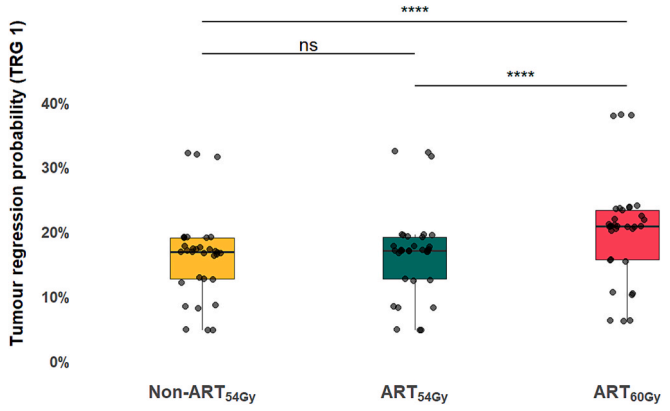

Fig. 2. Tumour regression probability comparison between Non-ART$_{54Gy}$, ART$_{54Gy}$, and ART$_{60Gy}$ based on the dose–response model developed by Appelt et al. 2013 [20]. **** $p < 0.0001$ ART: Adaptive radiotherapy, TRG: Tumour regression grade.

strategies for rectal boost. Unlike non-adaptive strategies, a random delineation error was added to the systematic delineation error since the CTV$_{Boost}$ is delineated daily, potentially by different operators [32]. Online adaptation allowed a PTV margin reduction of 10.9, 1.8, and 3.6 mm in the antero-posterior, left–right, and supero-inferior directions, respectively. Margins were larger in the antero-posterior and supero-inferior axes, consistent with other population-based PTV margin for rectal tumour [19,33,34]. Tumour motion (translation and deformation) accounted for most of the PTV margin. In the anterior-posterior axis, interfraction translation is much higher than the intrafraction translation motion, leading to an important difference between the non-adaptive and online-ART antero-posterior PTV margin. In addition to PTV reduction, online-ART (ART$_{54Gy}$ and ART$_{60Gy}$) achieved better target volume coverage than non-adaptive RT (Non-ART$_{54Gy}$) with a similar risk of organ-at-risk expected toxicities. With non-adaptive strategy, the PTV$_{Boost}$ coverage objective was not met in 87,9% of sessions, compared to only 12.1 % with online-ART. The PTV$_{Low}$, coverage was always achieved in online-ART sessions but only in 48.5 % of non-adaptive sessions. Regarding priority 1&2 OAR objectives, more violations occurred (even not significant, $p = 0.32$) with Non-ART$_{54Gy}$ (62/231) compared to ART$_{54Gy}$ (49/231), and ART$_{60Gy}$ (48/231). Furthermore, online-ART enabled dose-escalation, significant increasing the tumour regression probability without increasing toxicity risk. These results suggest that online-ART could increase the proportion of patients eligible for organ preservation strategy and, therefore, improve quality of life.

Additional strategies may further decrease PTV margins. For example, multi-modality imaging such as T2- or diffusion-weighted MRI and F-18 fluorodeoxyglucose positron emission tomography improves interoperator agreement in delineation [35–37]. Also, MRI-guided RT allows direct visualisation of the tumour and real-time ART. By tracking the tumour or repeating multiple non-irradiating images with the MRI system associated with a linear accelerator, the beam could be stopped when the tumour extends spatial tolerance limits to enable plan adaptation [33,38–41]. Kensen et al., 2023 reported PTV margins for MRI-guided boost of the primary tumour of 3.2, 5.6, 1.7, and 4.7 mm in the anterior, posterior, left–right, and supero-inferior directions, respectively [33]. While these values are even lower than ours, their boost volume included only the GTV, for which the tumour motion can be described only by the translation of the centre of mass of the tumour without considering the deformation component, and delineation errors [33]. Moreover, MR-linacs availability is limited, similarly to machines dedicated to CBCT-guided online ART, due important financial, time and human resources required [42].

The PTV reduction with CBCT-guided online-ART opens the door for more preservative treatments considering the dose–response relationship demonstrated in locally advanced colorectal cancer [20]. Also, high pCR rates with acceptable toxicities have been highlighted when increasing the dose to the primary rectal tumour above 60 Gy [3]. Therefore, delivering a higher dose to the primary tumour should be investigated in addition to the total neoadjuvant therapy, which already allows rectal preservation in up to 50 % of the patients [6,20]. One of the major limitations for dose escalation remains the dose delivered to the pelvic OARs. This could lead to an excess of RT-induced adverse events and a reduction of the quality of life compared with standard treatment [14]. By reducing the PTV margin, CBCT-guided online-ART could reduce the dose received by OARs and, therefore, possibly reduce the adverse events.

This study has limitations. First, the small number of patients limits the inclusion of other important parameters into our PTV margins. The patient gender, the treatment position, the treatment progress over time, the tumour location in the rectum, or the patient preparation can influence the rectal motion and, thus, the PTV margin values [15–19,43–45]. Particularly, there is an imbalance between male ($n = 10$) and female ($n = 1$), potentially underestimating PTV margin size in women, who present a higher systematic variation in the mesorectum shape [44]. Also, rectal motion is greatly impacted by session duration [41]. Kleijnen et al., 2016 used a cine-MRI in 16 patients for rectal tumour motion quantification. They reported that the intrafraction motion amplitude is similar interfraction motion amplitude after only 18 min [41]. While session duration is critical for online-ART, the workflow presented here should be adapted to reduce this duration as much as possible and limit the intrafraction motion impact [23,46,47]. Second, we used a rectal boost volume including the circumferential rectal wall, following major rectum RT trials [6,8]. In the absence of any consensus regarding boost delineation, PTV$_{boost}$ margins presented here could not be applicable for other teams, using different CTV$_{boost}$ definitions. Third, to homogenise the cohort, no RT boost was delivered to lymph node. While nodal boosts are common in practice, their PTV margin should be computed individually, as uncertainties may differ from those of the primary tumour. Fourth, the TRP model used, published in 2013, does not account for recent developments in LARC management, such as induction/consolidation chemotherapy or new molecular classifications predictive of treatment response [5,6,48,49]. Also, contemporary TRP results obtained after total neoadjuvant therapy are higher than those expected here [5,6,48]. Thus, TRP findings should be interpreted cautiously, focusing on relative improvements from dose escalation rather than absolute values.

External beam RT for rectal boost lacks clear consensus regarding the

definition of the volumes to be irradiated. The GTV_{boost} alone or added with a numeric or anatomical margin (such as the rectum or the mesorectum) could be considered an acceptable CTV_{boost} [6,8,9,11,50]. Definitions of the PTV are even more variable among different studies [6,9,11,15,50]. Using an empirical isotropic margin is widespread, often in the absence of an experimental or clinical rationale [6,9,11]. More comprehensive PTV definitions that compensate for interfraction rectal motion have also been described [15–17]. Other teams also proposed a PTV definition that integrates set-up and/or delineation errors in addition to the rectal motion [18,19]. However, these suggested margins remain considerable and their use results in a large total irradiated volume, which could lead to potential RT-induced toxicities for pelvic OARs.

In conclusion, we present a population-based PTV margin quantification for rectal boost RT. Compared to non-adaptive strategies, CBCT-guided online-adaptive RT allowed a reduction of this margin eliminating interfraction motion errors. Due to larger tumour motion, PTV margins were greater in the antero-posterior and supero-inferior axes, respectively, compared to the left right axis. This PTV reduction combined with daily adaptation allows a better target volume coverage with similar dose to OARs compared to non-adaptive strategies. Furthermore, when escalating the primary tumour dose, a better tumour control probability is expected with, again, a similar toxicity risk compared to non-adaptive strategy. Online-adaptive RT opens the door for a safe dose-escalation to the primary rectal tumour and, therefore, offering potentially more organ preservation in an increasing proportion of locally advanced rectal cancer patients.

CRediT authorship contribution statement

Julien Pierrard: Conceptualization, Methodology, Formal analysis, Software, Visualization, Writing – original draft. **David Dechambre:** Methodology, Writing – review & editing. **Geneviève Van Ooteghem:** Investigation, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2025.100757.

Data availability

Data will be share upon acceptable request to the corresponding author.

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