Technical Innovations & Patient Support in Radiation Oncology 6 (2018) 5–10

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.elsevier.com/locate/tipsro

Research article

Hybrid Tri-Co-60 MRI radiotherapy for locally advanced rectal cancer: An *in silico* evaluation

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ARTICLE INFO

Article history:
Received 25 November 2017
Received in revised form 26 February 2018
Accepted 26 February 2018
Available online 31 March 2018

ABSTRACT

Introduction: Aim of this paper is to investigate the plan quality of a tri-Co-60 MRI-Hybrid system for intensity-modulated radiation therapy (IMRT) in patients affected by locally advanced rectal cancer (LARC) undergoing neo-adjuvant radiotherapy.

Materials and methods: Ten consecutive LARC patients were selected. Tri-Co-60 step and shoot IMRT plans were generated simulating the presence of the magnetic field (B_{on}) or not (B_{off}) with the dedicated treatment planning system (TPS).

The total planned dose was 45 Gy in 25 fractions to the mesorectum and the pelvic nodes (planning target volume 2, PTV2) and 55 Gy to the tumor and correspondent mesorectum (PTV1) through simultaneous integrated boost (SIB). Tri-Co-60 IMRT plans were compared with Volumetric Modulated Arc Therapy (VMAT) and IMRT plans for Linear Accelerator (Linac).

Results: B_{on} and B_{off} tri-Co-60 IMRT plans showed no relevant differences. Mean values of PTV1 and PTV2 receiving at least 95% of the D_p ($V_{95\%}$) were higher than 95% in all treatment plans. All plans met the $V_{105\%}$ constraint for the PTV1. Mean values of $V_{105\%}$ for the PTV2 were 14.8, 5.0, and 7.3% respectively for tri-Co-60, VMAT and IMRT. Mean Wu's HI values were similar in all plans (7.4–7.8%). All plans met the V_{45Gy} constraint for small bowel, but mean V_{45Gy} value was higher with tri-Co-60.

Bladder irradiation was comparable and always lower than the chosen D max 65 Gy constraint.

Mean values of V_{5Gy} and V_{20Gy} to the body and median skin doses were higher with tri-Co-60 plans.

Discussion: Treatment plans with Tri-Co-60 step and shoot IMRT met the dose-volume objectives in patients with LARC. Nevertheless, a larger volume of normal tissue received low-moderate doses when compared with Linac based VMAT and IMRT.

Introduction

Radiation therapy (RT) has a crucial role in the multidisciplinary management of locally advanced rectal cancer (LARC), particularly in the neoadjuvant setting, where it reaches significant tumour downsizing, allowing more conservative surgical approaches and assuring significantly better clinical outcomes to the best responder patients who may avoid postoperative treatment intensification [1,2].

The technologies developed in the last decades, such as intensity modulated radiation therapy (IMRT) and volumetric arch therapy (VMAT) allow to tailor dose distributions with steep gradients on the target, potentially reducing the radiation damage to surrounding organs at risk (OaRs) and ensuring a safe dose delivery [3].

Previous studies about pelvic irradiation demonstrated that modern conformal techniques (such as the aforementioned IMRT and VMAT applications) can successfully reduce small bowel irradiation with promising gastrointestinal toxicity restraint results [4–8].

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https://doi.org/10.1016/j.tipsro.2018.02.002

Nevertheless, the evidence about the real benefits of the use of these advanced irradiation techniques in rectal cancer is scarce and their real impact on toxicity reduction, when compared to 3D conformal radiotherapy (3DCR) techniques, is still topic of debate [9–11].

However, pelvic organs are mobile structures and without the addition of appropriate geometrical margins, the benefits of these advanced techniques may be lost or even become detrimental.

In order to take into account such geometric uncertainty, the consensus Radiation Therapy Oncology Group (RTOG) guidelines for CTV delineation in rectal cancer suggest an isotropic margin of 0.7–1.0 cm for PTV definition [12].

In this frame, image-guidance techniques may reduce geometrical uncertainty potentially leading to an improvement of local control, minimising the geographical missing risk and the potential radiation damage to organs at risk, enabling in the meanwhile a margin reduction on the target volumes that could allow dose escalation protocols [13].

To date, image guidance based on electronic portal imaging device (EPID) is widely available, even if it relies only on bony anatomy while significant inter and intrafraction variations may occur in the position of the target and OaRs secondary to rectal and bladder filling [14,15].

The cone beam computed tomography (CBCT) better visualizes soft tissues, however, due to its inherent poor contrast resolution, difficulties in mesorectum delineation have been reported in literature also with this approach [15].

Magnetic resonance-imaging (MRI) appears therefore to be the image modality that offers and the best soft-tissue contrast and highest level of anatomical detail, discriminating tumours from their surrounding normal anatomy.

In addition, MRI is non-invasive and has no unnecessary radiation-exposure for patients.

The recently released MRIdian® system (ViewRay Inc., Cleveland, Ohio, USA) is a hybrid machine that consists in two main components: a 0.35 T whole body MRI scanner and a delivery system composed by three Cobalt-60 (tri-Co-60) sources with a dose rate of 550 cGy/minute, each connected to independent doubly focused multileaf collimators (leaf width 1.05 cm). The built-in MRI scanner allows the planar visualization and tracking of tumour and OaRs movements, assuring a more reliable visualization of the therapy volumes and achieving real time MRI based adaptive RT [16,17].

However, the treatment beam delivery system of this machine is relatively inferior to conventional linear accelerators (Linacs) due to the larger penumbra of the Co-60 sources, the lower penetrating power of gamma ray of the Co-60 photon beam and larger leaf width of the multileaf collimators [18].

Various studies on the tri-Co-60 IMRT plan quality have already been performed, describing its performance in several anatomical sites [19–22]; however, no investigations have been performed about rectal cancer.

Aim of this study is to perform an *in silico* evaluation of a tri-Co-60 IMRT planning system in LARC patients treated preoperatively.

This planning analysis represents a first proof of concept to verify the possibility to safely introduce MR guided hybrid treatments in clinical practice and could represent a dosimetric benchmark for the recently released hybrid MRIdian 6 MV linear accelerators (MRIdian Linac) that will shortly update and substitute the tri-Co-60 units.

Materials and methods

Patient selection

Ten consecutive patients affected by LARC who underwent neoadjuvant radio-chemotherapy in our Institution were retrospectively selected.

Five of them were men and five women; mean age was 62 years (range 55–70).

Patients' diseases were staged as cT3-T4 cN0-1 according to TNM 2009 version [23].

Simulation imaging acquisition, target volume definition and treatment planning

Simulation and imaging acquisition

A helical CT scanner (GE HiSpeed DX/i Spiral) was used for simulation CT imaging acquisition (slice thickness was 2.5 mm). Patients were scanned in supine position on a flat table-top, without specific bowel preparation and following a bladder filling protocol. No intravenous contrast has been used.

Target volume definition

The simulation imaging was manually segmented on Eclipse treatment planning system (TPS) (Eclipse®, Varian Medical Systems, Palo Alto, California, USA).

Target volumes were identified through the co-registration of the staging diagnostic MRI T2 weighted and 18-FDG PET-CT imaging with the CT simulation.

The clinical target volume (CTV) 1 included the visible tumour and the correspondent mesorectum, while the CTV2 was represented by the whole mesorectum and the regional drainage pelvic nodes. The planning target volumes 1 and 2 (PTV1-2) were generated adding a 0.7 cm isotropic margin to the CTVs.

The OaRs considered for this analysis included: body, skin, small bowel (contoured as intestinal cavity) and bladder.

Treatment planning: prescribed dose

The total prescribed dose was: 45 Gy (1.8 Gy per fraction) to the PTV2 and 55 Gy (2.2 Gy per fraction) to the PTV1 through simultaneous integrated boost (SIB) technique, according to our internal clinical protocol.

Treatment planning – Linac

Sliding windows IMRT and VMAT plans were calculated using 6 or 15MV photons.

Sliding windows IMRT plans were optimized using five coplanar beams (180°, 108°, 36°, 324° and 252°) with a dose rate of 400 MU/min and beam energy of 6 or 15 MV photons.

VMAT plans were performed with two full coplanar arcs sharing the same isocentre and delivered with opposite rotation (clockwise and counter-clockwise) with collimator of 45° and 315° respectively.

Sliding windows IMRT plans and VMAT plans were optimized through the Eclipse progressive resolution optimizer 3 algorithm (PRO3, ver. 10, Varian Medical Systems, Palo Alto, CA, USA).

The treatment plan optimization process aimed at the following dose-volume objectives: more than 95% of the PTVs should receive more than 95% of the prescription dose (D_p), and no more than 5% of the PTV1 should receive doses higher than 105% of the D_p.

A dose-volume constraint was set also to limit the $V_{105\%}$ of the PTV2.

On the OARs side, the following dose-volume constraints have been defined: V45 Gy less than 195 cc for small bowel (SB) and Dmax less than 65 Gy for the bladder, while no specific dose constraints has been applied for body and skin.

After optimization, dose distribution was calculated with the anisotropic analytic algorithm (AAA, ver. 11, Varian Medical Systems, Palo Alto, CA, USA) with a dose calculation grid of 2.5 mm for both techniques [24].

Treatment planning – MRIdian

The patients CT images and structure sets were imported to the MRIdian® TPS and tri-Co-60 IMRT step and shoot plans were generated.

The plans were computed with 21 equally-spaced non opposing beams divided into 7 groups of 3 fields each (triplets) simultaneously delivered. Two different scenarios of delivery were simulated: with (tri-Co-60 B_{on}) and without (tri-Co-60 B_{off}) the presence of the static 0.35 T magnetic field.

Coils were not considered in the calculation, as not present in CT simulation imaging. Monte Carlo algorithm was applied for dose calculation [25].

The values of the level and dose calculation grid were set to 15 and 0.3 cm, respectively. The optimization was performed with the same objectives as for the VMAT and IMRT planning.

Plan comparison

For target volumes, the endpoints compared among the different types of plans included: the percentage of PTVs receiving at least 95%, 100% and 105% of the D_p ($V_{95\%}$, $V_{100\%}$ and $V_{105\%}$); and the homogeneity index (HI).

The HI was calculated according to Wu and colleagues, as follows [26]:

$$(\mathrm{HI}) = \frac{D_{2\%} - D_{98\%}}{D_p * 100}$$

where $D_{2\%}$ and $D_{98\%}$ represent the minimum delivered doses to 2% and 98% of the PTV respectively, and D_p is the prescription dose. The ideal value of the Wu's HI should be 0 and it increases as the dose distribution becomes less homogeneous.

For OARs, the endpoints compared among different type of plans included the V_{45Gy} of the SB and the maximum dose to the bladder.

For the body, V_{5Gy} and V_{20Gy} were recorded to quantify normal tissue irradiation.

Furthermore, in order to investigate how much the dose delivered to the skin and subcutaneous tissues reflected the use of Co sources, the median dose in a 5 mm wide ring dummy volume contoured at a 3 mm depth from the body surface was calculated.

The outer 1 mm portion of the body was excluded from the analysis to avoid inconsistencies related to the uncertainty of dose calculation at air-body interface, as different dose calculation algorithms were used.

Statistical analysis

Mean values and standard deviations of dose-volumetric parameters were evaluated for each treatment technique.

Tukey multiple comparison of means test has also been calculated to compare VMAT to IMRT, tri-Co-60 to IMRT and tri-Co-60 to VMAT plans.

Differences characterized by p values less than 0.05 were considered statistically significant.

Data analysis was conducted with an in-house software named MODDICOM, realized with R platform (R software, version 3.1.2) [27].

Results

Four plans (Tri-Co-60 IMRT B_{on}; Tri-Co-60 IMRT B_{off}; IMRT; VMAT) were generated for each of the 10 evaluated patients (totaling 40 plans).

All plans met the dose-volumetric objectives for both target volumes and OARs.

B_{on} and B_{off} tri-Co-60 plans showed no relevant dosimetric differences and since the magnetic field is operating during treatment delivery with the MRIdian machine, only results of tri-Co-60 B_{on} were compared with VMAT and IMRT plans.

All the parameters took into account for the purposes of this analysis are shown in detail in Table 1 (target volumes) and Table 2 (OARs).

Results of the Tukey multiple comparison of means test are reported in Table 3.

Target volumes dose distribution comparison

PTV1 coverage and mean PTV1 $V_{95\%}$ were slightly higher with tri-Co-60 plans (98.9% for Tri-Co-60, 97.8% for VMAT and 98.2% for IMRT).

Comparable values were registered also for HI for the different techniques (7.0% for Tri-Co-60, 7.8% for VMAT and 7.7% for IMRT) and this difference appeared not to be statistically significant.

PTV1 $V_{105\%}$ was around zero for all techniques (0.1% for Tri-Co-60, 0.0% for VMAT and 0.1% for IMRT).

Mean $V_{95\%}$ values for the PTV2 were similar in all the different techniques (98% for Tri-Co-60, 98.4% for VMAT and 97.7% for IMRT), while a slight worse performance of tri-Co-60 plans has been observed for the $V_{105\%}$ (14.7% for Tri-Co-60, 5% for VMAT and 7.3% for IMRT) and HI index (20% for Tri-Co-60, 13.26% for VMAT and 14.69% for IMRT).

Average DHVs for PTV1 and PTV2 are shown in Fig. 1.

OARs dose distribution comparison

The analysis of OARs irradiation showed higher mean V_{45Gy} values to the SB with tri-Co-60 (70.1 cc for Tri-Co-60, 10.6 cc for VMAT and 48.7 for IMRT), while comparable values have been registered for the bladder in terms of Dmax (48.7 Gy for Tri-Co-60, 48.2 Gy for VMAT and 50.4 Gy for IMRT).

Although the median skin dose had small absolute values (less than 2 Gy in all treatment plans), it nearly doubled in the tri-Co-60 plans (1.95 Gy for Tri-Co-60, 1.0 Gy for VMAT and 0.98 Gy for IMRT).

Similarly, mean V_{5Gy} and V_{20Gy} values of the body were higher in tri-Co-60 plan.

Fig. 2 provides an example of the dose distribution calculated with the different techniques, showing the larger portion of body encompassed by the 20 Gy isodose line in the tri-Co-60 plan.

Discussion

This study is an *in silico* evaluation of the treatment plan quality reached by a tri-Co-60 treatment unit in patients undergoing long course pre-operative chemoradiotherapy for LARC.

In all cases, the tri-Co-60 step and shoot IMRT plans met the dose-volumetric objectives for both the target and the OARs, however plan quality was slightly worse as compared to Linac VMAT and IMRT plans, especially on the low dose OARs side.

The majority of the few previously published tri-Co-60 RT studies have dealt with small target volumes treated with hypofractionated high dose stereotactic radiotherapy. As an example, Kishan and colleagues compared eleven SBRT plans for liver lesions (prescription doses ranging between 36 and 60 Gy, in 3–5 fractions) and observed good target coverage with the exception of residual liver and skin which appeared to be exposed to low radiation doses [28].

Merna et al. analysed 20 SBRT plans for lung lesions (prescription doses of 50 Gy in 4 fractions) and observed comparable target

Table 1
Target volumes dosimetric comparison mean values.

	V95%PTV1	V105%PTV1	V95%PTV2	V100%PTV2	V105%PTV2	HI PTV1	HI PTV2
Tri-Co-60 B_{on}	98.9 Range (97.4–99.6) SD ± 0.78%	0.14 Range (0–0.4) SD ± 0.15%	98.0 Range (97.4–98.5) SD ± 0.4%	55.8 Range (55.83–64.86) SD ± 3.33%	14.7 Range (7.12–21) SD ± 5.47%	7.0% Range (5–9) SD ± 1%	20% Range (16–21) SD ± 2%
Tri-Co-60 B_{off}	99.2 Range (98.7–99.7) SD ± 0.39%	0.0 Range (0.0) SD 0.0%	98.2 Range (97.6–98.8) SD ± 0.46%	62.0 Range (59.1–66) SD ± 2.7%	14.8 Range (6.76–20.9) SD ± 5.9%	7.4% Range (6.8–8) SD ± 0.41%	20.04% Range (16.07–22.09) SD ± 2.07%
VMAT	97.8 Range (95.7–99) SD ± 1.15%	0.0 Range (0.0) SD 0.0%	98.4 Range (95.8–99.5) SD ± 1.29%	47.3 Range (42.9–57.6) SD ± 6.44%	5.0 Range (1.36–8.6) SD ± 2.8%	7.82% Range (6.8–8.7) SD ± 0.72%	13.26% Range (8.29–17.30) SD ± 3.29%
IMRT	98.2 Range (97–99) SD ± 0.76%	0.1 Range (0–0.96) SD ± 0.35%	97.7 Range (95.3–99.9) SD ± 1.58%	54.8 Range (47.6–68.5) SD ± 7.1%	7.3 Range (1.31–10.43) SD ± 3.31%	7.72% Range (6.7–9.3) SD ± 0.96%	14.69% Range (5.35–19.80) SD ± 4.76%

Legend: VMAT: Volumetric Modulated Arc Therapy; IMRT: Intensity Modulated Radiation Therapy; Tri-Co-60 IMRT-MRI: 60 Cobalt-Magnetic Resonance Imaging; B_{on}: with magnetic field presence; B_{off}: without magnetic field presence; HI: Homogeneity index; PTV: Planning Target Volume; Gy: Gray; SD: standard deviation.

Table 2
Organs at risk dosimetric comparison.

	V5 Body (cm^3)	V20 Body (cm^3)	V45 Bowel (cm^3)	Max dose bladder (mean values, Gy)	Median skin dose (Gy)
Tri-Co-60 B_{on}	12,678 Range (10969–14581) SD ± 1906.6	6589 Range (5893–7688) SD ± 613.9	70.1 Range (5.3–128) SD ± 43.6	48.7 Range (44.5–56.0) SD ± 3.9	1.95 Range (1.03–2.53) SD ± 0.45
Tri-Co-60 B_{off}	12,809 Range (11090–15907) SD ± 1847.8	6871 Range (6126–7491) SD ± 566.6	59.4 Range (6.84–114.7) SD ± 36.0	50.2 Range (46.6–55.7) SD ± 3.5	1.97 Range (1.1–2.97) SD ± 0.54
VMAT	10,826 Range (8986–13677) SD ± 1729.2	4559 Range (3792–5787) SD ± 730.7	10.6 Range (3–71.3) SD ± 23.3	48.2 Range (44.3–55.2) SD ± 4	1.0 Range (0.52–1.65) SD ± 0.35
IMRT	10,039 Range (8451–12410) SD ± 1487	5901 Range (4591–7738) SD ± 1071	48.7 Range (9.6–272.2) SD ± 93.4	50.4 Range (45.4–54.6) SD ± 3.85	0.98 Range (0.57–1.48) SD ± 0.27

Legend: VMAT: Volumetric Modulated Arc Therapy; IMRT: Intensity Modulated Radiation Therapy; tri-Co-60 IMRT-MRI: 60 Cobalt-Magnetic Resonance Imaging; B_{on}: with magnetic field presence; B_{off}: without magnetic field presence; Gy: Gray; SD: standard deviation.

Table 3
p values of the Tukey multiple comparison of means test.

	V5 Body (cm^3)	V20 Body (cm^3)	V45 Bowel (cm^3)	Max dose bladder (max values, Gy)	Median skin dose (Gy)	HI PTV1	HI PTV2
VMAT-IMRT	0.66	0.01 (S)	0.34	0.51	0.99	0.96	0.73
Tri-Co-60 –VMAT	0.10	0.0001 (S)	0.52	0.88	0.0006 (S)	0.69	0.02 (S)
Tri-Co-60 – IMRT	0.01 (S)	0.09	0.94	0.80	0.0006 (S)	0.54	0.005 (S)

Legend: VMAT: Volumetric Modulated Arc Therapy; IMRT: Intensity Modulated Radiation Therapy; Tri-Co-60: 60 Cobalt; HI: Homogeneity index; PTV: Planning Target Volume; Gy: Gray; (S): significant ($p \leq 0.05$).

coverage with worse OARs sparing, as compared with linac plans (especially for the low dose to the lung) [29].

Few studies investigated the use the tri-Co-60 MRI technology for long course treatments with standard fractionation and larger therapy volumes: Kishan et al. evaluated the dosimetric performance of a tri-Co-60 treatment unit in soft tissue sarcomas of the extremities (prescription dose of 50 Gy in 25 fractions) and observed that plan quality was comparable with Linac plans [30].

Saenz and colleagues compared *in silico* tri-Co-60 treatments with standard Linac plans for long course treatments in various sites, including pelvic tumors, and came to the conclusion that this new technology can achieve Linac-quality treatments with minor increase of target coverage heterogeneity and generally higher low-dose OARs irradiation [31].

In agreement with the aforementioned colleagues, also in the present series of LARC patients, the tri-Co-60 IMRT plans achieved almost equivalent target coverage and dose homogeneity when compared to Linac plans, while the doses to OARs were slightly higher.

The tri-Co-60 PTV2 $V_{105\%}$ resulted to be higher as compared to Linac techniques: this suboptimal result is probably related both to a reduced possibility of the tri-Co-60 unit to generate steep dose gradients because of the large width of the MLC leaves (1.05 cm) and to the low priority usually given during the treatment plan optimization process to such dose-volumetric object.

The increased median skin dose and body irradiation with the tri-Co-60 technique represent one of the major limits of this technology and can be easily explained by the lower energy of the Co-60 photons as compared to Linac ones.

On the other hand, its benefits mainly consist of the possibility to use new and more precise IGRT protocols, that can also take advantage of the on board MR functional imaging techniques.

As an example, the use of Diffusion Weighted imaging (DWI) could allow fully personalized radiation treatment delivery for

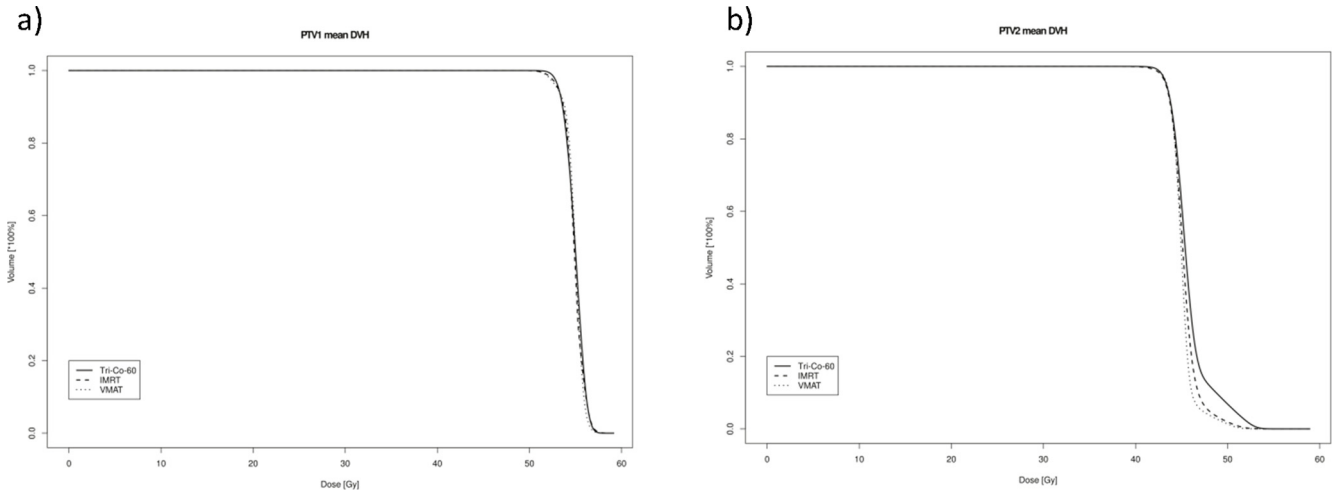

Fig. 1. Average DVHs for target structures: PTV1 (a) and PTV2 (b).

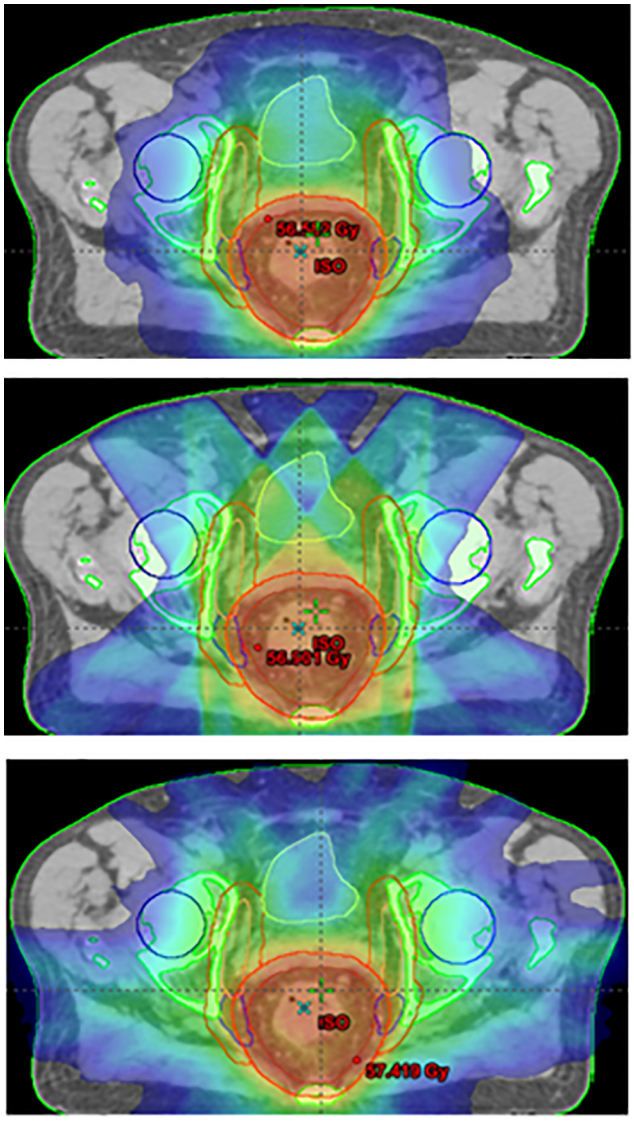

Fig. 2. Dose color-wash distribution with a 20 Gy threshold obtained with VMAT (top), IMRT (middle) and tri-Co-60 B_{off} (down).

LARC, both in terms of dose escalation or treatment de-intensification.

The variation of the apparent diffusion coefficient (ADC) during treatment showed promising results in the assessment of early response and even as predictor of treatment's outcome [32].

Furthermore, the use of such advanced imaging techniques, that provide a reliable morphological and biological visualization of therapy volumes, can successfully be integrated in hybrid MR guided dose escalation protocols able to reduce unintended irradiation of the organs at risk, while maximizing in the same time the dose to the target [33–36].

Park et al. compared tri-Co-60 IMRT plans with standard practice VMAT ones for cervical cancer long course treatments (prescription dose 50.4 Gy in 28 fractions) and, interestingly, they observed a better overall quality of the tri-Co-60 IMRT plans, with several advantages with regards to normal tissue irradiation (statistically significant advantages were reported in the tri-Co-60 IMRT plans comparison with the VMAT ones with p values lower than 0.001).

These significant advantages are mainly related to the reduced margin used in the tri-Co-60 IMRT plans, confirming the promising performances of hybrid MRI guided radiotherapy in terms of target volume margin reduction, as an isotropic CTV to PTV margin of 1 mm has been used instead of the expansion of 0.7 cm in all directions and of 1 cm in the anterior-posterior axis, routinely added to CTV in the VMAT plans [21].

As reported by the mentioned planning experiences, the actual advantages of the hybrid MRI guided radiotherapy technology should be explored in further *in vivo* studies that should take into account the possibility to significantly reduce target margins thanks to the high-quality setup MR imaging.

These imaging advances, coupled with the fully online adaptive delivery workflow and the promising dosimetrical improvement of the MRIdian Linac update, will further enhance the clinical outcome of hybrid MR-RT treatments in LARC, especially in those cases in which high dose escalation protocols could avoid radical surgery approaches and preserve patients' quality of life.

In conclusion, this dosimetric comparison showed that tri-Co-60 MRI systems can provide acceptable plans for neoadjuvant RT delivered with SIB technique in LARC patients, even if larger volumes of normal tissue receive higher low-moderated doses, when compared with standard Linac VMAT and sliding window IMRT plans.

In this context of innovation and rapid progress, the creation of dedicated users consortium is strongly advocated to foster clinical research in this field through the definition of a common lexicon which could be of great help to face this new challenge and understand its real advantages and pitfalls [37].

Conflict of interest

The authors declared that there is no conflict of interest.

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