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ORIGINAL ARTICLE

Dose summation and image registration strategies for radiobiologically and anatomically corrected dose accumulation in pelvic re-irradiation

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ABSTRACT

Background: Re-irradiation (reRT) is a promising technique for patients with localized recurrence in a previously irradiated area but presents major challenges. These include how to deal with anatomical change between two courses of radiotherapy and integration of radiobiology when summating original and re-irradiation doses. The Support Tool for Re-Irradiation Decisions guided by Radiobiology (STRIDeR) project aims to develop a software tool for use in a commercial treatment planning system to facilitate more informed reRT by accounting for anatomical changes and incorporating radiobiology. We evaluated three approaches to dose summation, incorporating anatomical change and radiobiology to differing extents.

Methods: In a cohort of 21 patients who previously received pelvic re-irradiation the following dose summation strategies were compared: (1) Rigid registration (RIR) and physical dose summation, to reflect the current clinical approach, (2) RIR and radiobiological dose summation in equivalent dose in 2 Gy fractions (EQD2), and (3) Patient-specific deformable image registration (DIR) with EQD2 dose summation.

Results: RIR and physical dose summation (Strategy 1) resulted in high cumulative organ at risk (OAR) doses being 'missed' in 14% of cases, which were highlighted by EQD2 dose summation (Strategy 2). DIR (with EQD2 dose summation; Strategy 3) resulted in improved OAR overlap and distance to agreement metrics compared to RIR (with EQD2 dose summation; Strategy 2) and was consistently preferred in terms of clinical utility. DIR was considered to have a clinically important impact on dose summation in 38% of cases.

Conclusion: Re-irradiation cases require individualized assessment when considering dose summation with the previous treatment plan. Fractionation correction is necessary to meaningfully assess cumulative doses and reduce the risk of unintentional OAR overdose. DIR can add clinically relevant information in selected cases, especially for significant anatomical change. Robust solutions for cumulative dose assessment offer the potential for future improved understanding of cumulative OAR tolerances.

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Reirradiation; deformable image registration; EQD2; dose summation; personalisation

Introduction

There is an increasing interest in the use of re-irradiation (reRT) in patients, who experience limited cancer recurrence in a previously irradiated area [1]. Despite this, re-irradiation remains a complex technique, primarily due to two major challenges. Firstly, when determining which doses can safely be delivered to portions of previously irradiated organs at risk (OAR), anatomical changes between treatment courses should be taken into account. Such changes could result from surgery, change in habitus, patient positioning, organ filling, and internal motion. Secondly, combined doses between two treatment plans cannot simply be summated based on physical dose, despite this being the standard method in current commercial treatment planning systems. Instead, voxel-wise radiobiological conversion is necessary for meaningful dose-summation, as dose and dose-per-fraction vary with location, especially near the original steep dose gradient, where marginal and nodal recurrences (potential targets for reRT) commonly occur [2–4]. Consistent application of cumulative dose constraints is therefore challenging and has limited clinical uptake of reRT in loco-regionally recurrent disease. ReRT trials are largely absent, standard protocols are lacking and clinical practice is highly heterogeneous [5].

The **S**upport **T**ool for **R**e-**I**rradiation **De**cisions guided by **R**adiobiology (STRIDeR) project aims to improve reRT planning by considering (i) radiobiological dose summation, to account for differences in voxel-wise fraction size and (ii) optimized deformable image registration (DIR) were necessary to account for anatomical change. This paper primarily addresses the impact of the radiobiological dose summation and integration of DIR on cumulative dose assessment in the

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Supplemental data for this article can be accessed here.

pelvic re-irradiation setting using the tools available within a commercial treatment planning system.

Material and methods

Patient cohort

Twenty-one consecutive patients (18 male, 3 female) receiving stereotactic ablative body radiotherapy (SABR) reRT for nodal or bone oligometastases within the previously irradiated pelvis were included. Eligibility required: $\geq$6 month interval between original RT and recurrence, performance status $\leq$2, $\leq$3 oligometastatic lesions, no significant toxicity from previous RT, no significant bowel disease, and lesions $<$6 cm and full DICOM data for original RT [6]. Cases were discussed by a dedicated multi-disciplinary team. Patients had previously received radical-intent (chemo-) RT for colorectal ($n = 4$) or prostate ($n = 17$) cancer. Original RT doses ranged from 25 to 76 Gy in 5–37 fractions, 1–8 years previously, at various UK centers. Baseline characteristics are shown in Table 1.

Imaging and patient setup

Original RT setup varied according to (historical) local protocols and included prone and supine techniques. For SABR reRT, patients were immobilized supine using BodyFix (Elekta AB, Stockholm, Sweden), typically with an empty bladder for patient comfort.

Clinical reRT dose planning

Clinically delivered reRT doses for this retrospective cohort were planned according to local protocol. The original CT and dose were rigidly registered to the reRT CT, focusing on the reRT PTV. The maximum original dose, to a sub-volume of the OAR nearest to the reRT PTV, was used to represent the previous OAR dose for reRT planning. These doses were used to calculate the remaining tolerable OAR doses for SABR reRT (based on biologically effective dose (BED)), using the constraints specific to the NHS Commissioning through Evaluation (CtE) programme [6] (provided as dose in five fractions) as cumulative maxima (Supplementary Table 1). If OAR dose remaining was, in the clinician's opinion, too low for meaningful SABR reRT delivery *within CtE,* at the clinician's discretion, a degree of repair could be assumed and/or PTV coverage compromised. The intended reRT PTV $D_{95\%}$ prescription was 30 Gy in five alternate-weekday fractions. Decisions regarding the need to incorporate repair in order to improve coverage or/and accept a degree of under-coverage were taken on a case by case basis, with no set definition of when either approach should be adopted or how much repair was appropriate, reflecting the heterogeneity and uncertainty as to what represents optimal re-irradiation practice[5]. When repair was incorporated, this was done by subtracting only a proportion of the previous dose from the cumulative constraint (e.g., if 25% repair was assumed, then only 75% of the previous dose was subtracted from the cumulative constraint).

Retrospective dose summation

Retrospectively, original and reRT doses, as delivered clinically, were summed in three ways (Strategies 1 to 3; Figure 1):

Strategy 1. Rigid registration (RIR), driven by bony structures, and physical dose summation, to reflect the current standard clinical approach to dose summation

Strategy 2. Rigid registration and radiobiological dose summation

Here both the original dose distribution and the reRT dose distribution were each converted voxel-wise to equivalent dose in 2 Gy fractions (EQD2) according to:

$$\mathrm{EQD2} = \mathrm{D}\left(\frac{\mathrm{d} + (\alpha/\beta)}{2 + (\alpha/\beta)}\right)$$

where D is total dose, d is dose per fraction, α/β is fraction size sensitivity (3 Gy for all OAR tissues, except nerves, where $\alpha/\beta = 2$ Gy) [7]. As the original tumour was not re-irradiated, tumour-specific α/β ratios were not required. EQD2 dose distributions (original and reRT) were summed based on the rigid registration prior to evaluation of summary DVH statistics.

Strategy 3. Deformable image registration and radiological dose summation

DIR methodology and quality assessment: Both the Hybrid and Biomechanical (BM-DIR) DIR solutions available in RayStation 9B (RaySearch AB, Stockholm), together with a bespoke combined approach (Supplementary Figure 1), were investigated to determine the optimal patient-specific method for DIR (Supplementary Figures 1 and 2 and Supplementary Text). In brief, the optimal method was determined based on changes in bladder filling between treatment courses: a hybrid DIR method produced best results when the reRT bladder-volume was $>$80% of that at original RT and a novel combined (inverted hybrid + biomechanical) DIR approach was found to be optimal when the reRT bladder-volume was $<$80% of that at original RT. While the bladder itself was not necessarily an OAR of particular concern in every reRT case, correction for bladder filling, which drives pelvic anatomical changes, also improved the approximation of bowel position. As the re-irradiation targets in this cohort were not targets at original RT, an assessment for changes in target position between radiotherapy courses was not performed.

Quantitative methods of DIR quality assessment included inspection of the Deformation Vector Field Jacobian for negative (folded) elements and evaluation of Dice Similarity Coefficient (DSC), Mean Distance to Agreement (MDA), Hausdorff Distance (HD), precision, sensitivity and specificity, and Greyscale correlation-coefficient.

In addition, DIR quality was assessed visually by two expert clinical oncologists using a 5-point qualitative Likert scale to assess utility compared to RIR (compared to RIR: -2 = DIR substantially poorer, -1 = DIR somewhat poorer, 0 = equivalent, $+1$ = DIR somewhat improved, and $+2$ = DIR substantially improved). Factors considered in the assessment of utility included physical deformation plausibility, local

Table 1. Baseline characteristics.

Patient	Primary tumour type	Original RT dose (Gy)/ fractionation	Time interval to re-irradiation (months)	Site of recurrence	Maximum isodose from original radiotherapy with which re-irradiation PTV overlaps (%; based on rigid registration)	OAR(s) closest to re-irradiation PTV (vessels excluded as not dose limiting)
1	Rectal	25/5	43.2	Common iliac node	102.4	Small bowel
2	Prostate	52.5/20	34.2	Side wall node	9.3	Small bowel
3	Prostate	76/37	66.9	Ischium	90.0	Rectum
4	Rectal	50/25	52.3	Pre-sacral node	95.2	Small bowel and sacral plexus
5	Prostate	74/37	55.6	Common iliac node	4.3	Small bowel
6	Prostate	52.5/20	50.0	Side wall node (obturator)	18.1	Colon and sacral plexus
7	Rectal	50.4/28	85.3	Side wall node	102.4	Bladder
8	Prostate	38/15 (plus brachytherapy)	43.4	Side wall node (obturator)	69.9	Small bowel and colon
9	Prostate	76/37	60.9	Side wall node	4.9	Colon and sacral plexus
10	Prostate	60/20	66.3	Side wall node	5.0	Colon
11	Prostate	52.5/20	45.2	Side wall node (x2)	80.2	Colon, small bowel and sacral plexus
12	Prostate	52.5/20	32.3	Side wall node (EI)	5.1	Small bowel
13	Rectal	45/25	16.1	Pre-sacral node	11.5	Small bowel
14	Prostate	36/13 (plus brachytherapy)	81.3	Side wall node (EI)	4.5	Small bowel
15	Prostate	38/15 (plus brachytherapy)	48.5	Side wall node	85.6	Rectum, colon and sacral plexus
16	Prostate	55/20	15.4	Sacrum	2.4	Small bowel
17	Prostate	52.5/20	52.4	Acetabulum	15.1	Sacral plexus
18	Prostate	55/20	94.7	Side wall node (obturator)	54.4	Colon
19	Prostate	52.5/20	80.4	Side wall node	10.1	Small bowel
20	Prostate	66/33	34.9	Ischium	5.7	Rectum
21	Prostate	52.5/20	81.6	Side wall	7.4	Small bowel and sacral plexus

Abbreviations: EI: external iliac.

quality around the reRT PTV and dosimetric significance of DIR uncertainty, based on relative position of the original and reRT field gradients.

Radiobiological dose summation was performed as for 2 above, and EQD2 dose distributions (original and reRT) were summed based on the patient-specific DIR deformation map.

Dosimetric impact assessment

The dosimetric impact for each of the three approaches to dose summation was analysed *via* the change in a range of clinically relevant DVH statistics ($D_{0.5\,cm^3/0.1\,cm^3}$, $D_{5\,cm^3}$, and $D_{10\,cm^3}$; see Supplementary Table 1) [6].

Computational tools

All registrations, EQD2 conversions and dose summations were implemented using the scripting tools within RayStation 9B.

Results

This heterogeneous 21 patient cohort of pelvic reRT patients exhibited various, but typical, clinical features which complicated reRT dose accumulation: four had pelvic surgery in between original radiotherapy and reRT, two were originally treated prone, but received reRT supine. The distribution of bladder-volume change was bimodal, depending on bladder-filling protocol at original RT, with 15/21 patients showing a reRT bladder-volume $<$ 80% (34%–73%) of the original volume. On rigid registration (i.e., without consideration of changes in OAR position between treatment courses) and based on physical doses, the median isodose of overlap between the original dose and reRT PTVs was 11.3% (range (2.4%–102%) of the original prescription dose.

Impact of EQD2 dose summation (strategy 2 vs. Strategy 1)

Summated doses based on each of the three methods are summarized in Tables 2 and 3. Given the use of SABR for reRT, with physical dose summation (and RIR; Strategy 1), the biological impact of the high dose per fraction is masked, resulting in comparatively lower summated maximum ($D_{0.5\,cm^3}$) and threshold volume ($D_{5\,cm^3}$, $D_{10\,cm^3}$) doses compared to summation in EQD2 (and RIR; Strategy 2). By incorporating EQD2 into dose summation (Strategy 2), the impact of fraction size becomes apparent, with calculated maximum cumulative doses exceeding 90 Gy EQD2 in at least one organ in three out of 21 patients, including one patient (Patient 4) where cumulative EQD2 to 0.5 cm^3 of small bowel ($D_{0.5\,cm^3}$) was 107.6 Gy and cumulative sacral plexus EQD2 $D_{0.1\,cm^3}$ was 119.5 Gy (based on RIR and physical dose summation (Strategy 1) reported as 78.9 Gy and 79.2 Gy

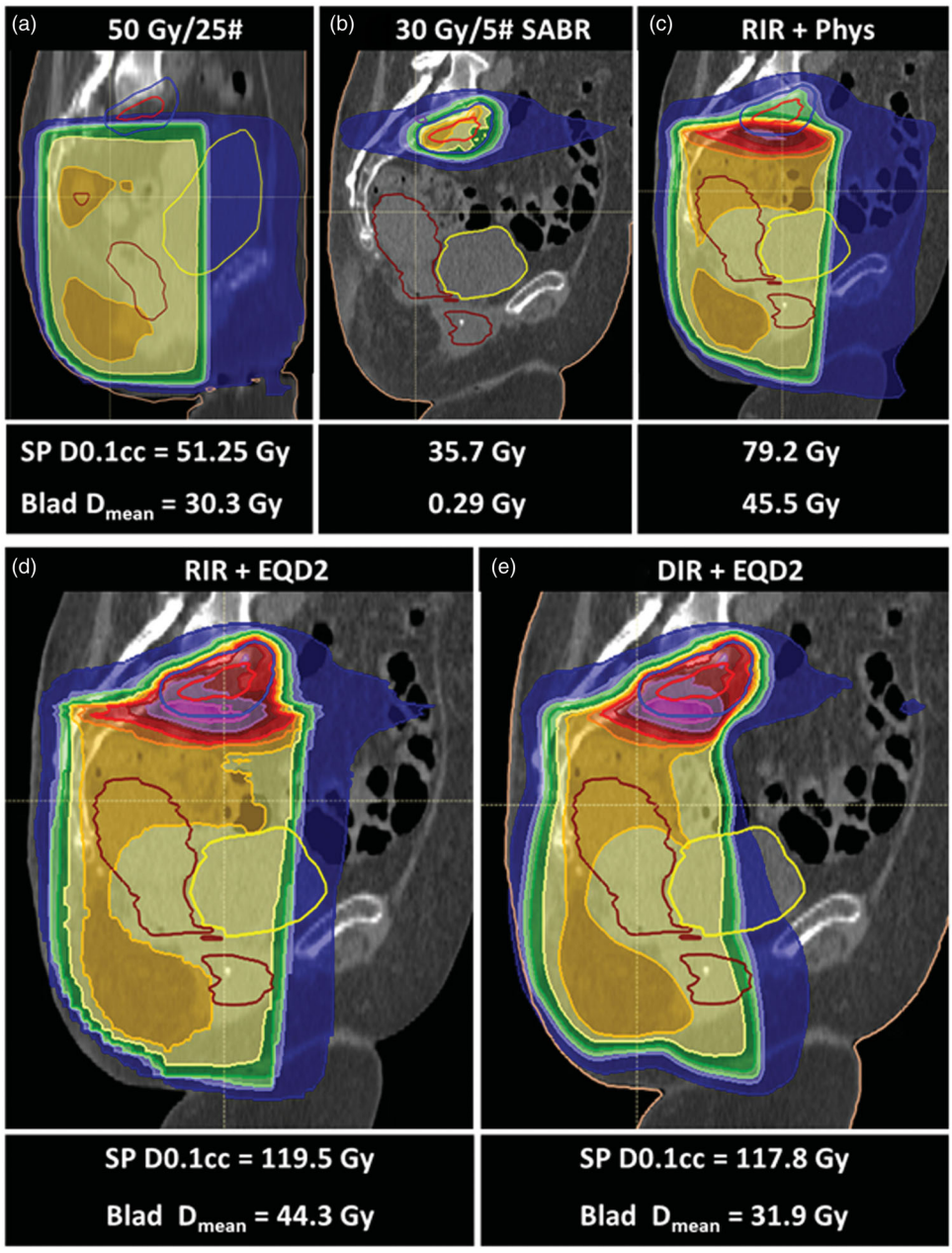

Figure 1. Example of workflow. (a) Original RT dose, (b) SABR reRT dose, (c) physical dose summation based on RIR (as routinely produced in most TPSs when evaluating cumulative doses), (d) per-voxel EQD2 dose summation with RIR and, (e) per-voxel EQD2 summation with STRIDeR combined DIR. Sacral plexus near-maximum dose (SP $D_{0.1\ cm^3}$) summation depends critically on EQD2 conversion and is independent of DIR as expected for a fixed structure. Conversely, mean bladder dose (Blad D_{mean}) is weakly dependent on EQD2 summation as SABR dose to the bladder is minimal, but depends strongly on DIR due to bladder-volume change on reRT. DIR with EQD2 summation is most representative of the combined dose delivered to the patient.

respectively; see Supplementary Table 1 for CtE dose limits). While the optimal cumulative normal tissue constraints for re-irradiation are not well defined, representing one of the major challenges of re-irradiation [5,8], the magnitude of these cumulative doses were not appreciated at the time of clinical plan prescription, when summated doses were assessed using physical dose summation and RIR. In the other two cases with cumulative EQD2 $>$ 90 Gy in normal tissues, one (Patient 7) showed combined bladder EQD2 $D_{0.5\ cm^3}$ of 110.1 Gy and the other (Patient 1) exhibited combined small bowel EQD2 $D_{0.5\ cm^3}$ of 96.9 Gy (based on Strategy 1 reported as 82.8 Gy and 55.7 Gy, respectively).

Impact of DIR on radiobiological dose summation (strategy 3 vs. Strategy 2)

Detailed results of quality assessment for DIR are provided in Supplementary Material (Supplementary Table 2, Supplementary Figures 3–4 and Supplementary text on DIR Results). In brief, overlap and distance to agreement metrics were consistently improved using DIR compared to RIR, most notably for bladder deformation, where the median Dice Similarity Co-efficient was 0.97 (compared to 0.43 using RIR), with simultaneous improvements in registration metrics for other OARs.

Table 2. Maximum doses to 0.5 cm^3 (median and range).

	Strategy 1 RIR and physical summation (Gy)	Strategy 2 RIR and EQD2 summation (Gy)	Strategy 3 STRIDeR DIR and EQD2 summation (Gy)
Small bowel	36.76 (6.06–78.90)	54.01 (4.43–107.60)	50.51 (4.18–106.35)
Colon	44.03 (5.37–66.55)	49.34 (4.02–79.17)	47.92 (4.13–74.66)
Rectum	53.93 (26.31–79.12)	61.16 (42.14–80.98)	60.14 (42.10–81.44)
Vessels	35.76 (27.33–79.34)	63.08 (39.38–116.56)	62.64 (37.08–114.97)
Sacral plexus*	42.04 (23.69–79.21)	57.69 (23.46–119.54)	57.41 (23.68–117.82)
Cauda equina*	12.03 (1.53–34.14)	12.49 (0.73–65.78)	12.48 (0.79–65.82)
Bladder	54.16 (33.99–82.83)	61.47 (41.15–110.15)	61.15 (41.30–110.66)

* Maximum dose reported to 0.1 cm^3 for neural structures.

Table 3. Dose to threshold volume (median and range).

	Threshold volume	Strategy 1 RIR and physical summation (Gy)	Strategy 2 RIR and EQD2 summation (Gy)	Strategy 3 STRIDeR DIR and EQD2 summation (Gy)
Small bowel	5 cm^3	24.06 (4.59–70.15)	30.99 (3.21–85.2)	22.52 (2.95–76.60)
Sacral plexus	5 cm^3	26.52 (11.20–62.28)	27.50 (9.06–82.54)	26.14 (9.52–84.07)
Cauda equina	5 cm^3	14.58 (2.41–21.24)	14.27 (1.26–31.85)	14.13 (1.24–31.88)
Bladder	15 cm^3	53.15 (26.84–72.16)	59.80 (39.79–79.82)	59.38 (34.65–79.95)
Left femoral head	10 cm^3	35.92 (18.63–49.09)	33.09 (16.91–45.58)	32.81 (16.78–46.64)
Right femoral head	10 cm^3	35.50 (7.75–53.62)	33.87 (5.54–46.33)	33.50 (5.54–46.16)

Expert assessment on a 5-point Likert scale found clinical utility for dose-summation in reRT was 'substantially improved' by patient-specific DIR in 9/21 cases and 'somewhat improved' in the remaining 12 cases, with DIR never considered equivalent to or worse than RIR. Clinicians noted, however, that while DIR was consistently preferable, beyond the recto-sigmoid-descending portion of colon, large and small bowel matching was not reliable at a loop-to-loop level.

The quantitative dosimetric impact of the integration of DIR, in addition to EQD2 correction, for dose summation (i.e., Strategy 3) is variable and influenced by the specific OAR in question (Tables 2 and 3, Supplementary Table 2 and Supplementary Figures 3–4). Additionally, the dosimetric impact of DIR was most clearly visualized in cases where the bladder had a markedly reduced volume at reRT compared to during the original course of radiotherapy (examples shown in Figures 1 and 2). In this situation tissue previously outside the original RT field, moves into the geometric region of the original RT dose at reRT, when the bladder is empty. The DIR correctly maps the fact that the antero-superior bladder wall and adjacent bowel loops, now positioned more posteriorly and inferiorly in the pelvis, were typically not previously irradiated to high dose.

Substantial dose differences (>10 Gy EQD2 for OAR maximum/threshold volume doses) were observed with DIR (and EQD2 correction; Strategy 3) vs. RIR (and EQD2 correction; Strategy 2) in 11/21 (52%) cases, although such magnitudes of change were not always considered of clinical significance (see below). The most common dose-summation impacting scenarios were gross changes in bladder filling and the presence of rectal gas on the reRT scan. Whilst bladder volume reduction at reRT tended to reduce combined OAR (colon and/or small bowel) doses, as described above, correctly modelling bowel gas tended to push previously irradiated tissue beyond the confines of the original RT field, towards the reRT target. In both cases, the DIR derived dose distributions were more realistic, but the combined EQD2 DVH statistics with DIR were typically lower than with RIR in the case of bladder filling reduction (Figure 2) and higher than with RIR where rectal gas causes a degree of deformation (Figure 3). More immobile OARs (e.g., femoral heads, cauda equina, sacral plexus, and vessels) did not undergo significant deformations and hence did not exhibit substantial dosimetric differences with DIR compared to RIR (which is driven by bony matching; Tables 2 and 3, Figure 1).

In our 21 patient cohort, we observed eight cases (38%) where anatomical changes, appropriately modelled by DIR (within Strategy 3), resulted in dosimetric changes in that were considered of clinical relevance; based on the assumption that cumulative bowel doses up to ~50 Gy EQD2 are clinically acceptable, as these are within constraints for both *de novo* SABR (Supplementary Table 1) and conventionally fractionated irradiation. This level of dose overlap also represents sufficient geometric margin from the steep SABR dose gradient, minimizing the risk of excessive cumulative doses (e.g., >90 Gy EQD2) where safety is less well established.

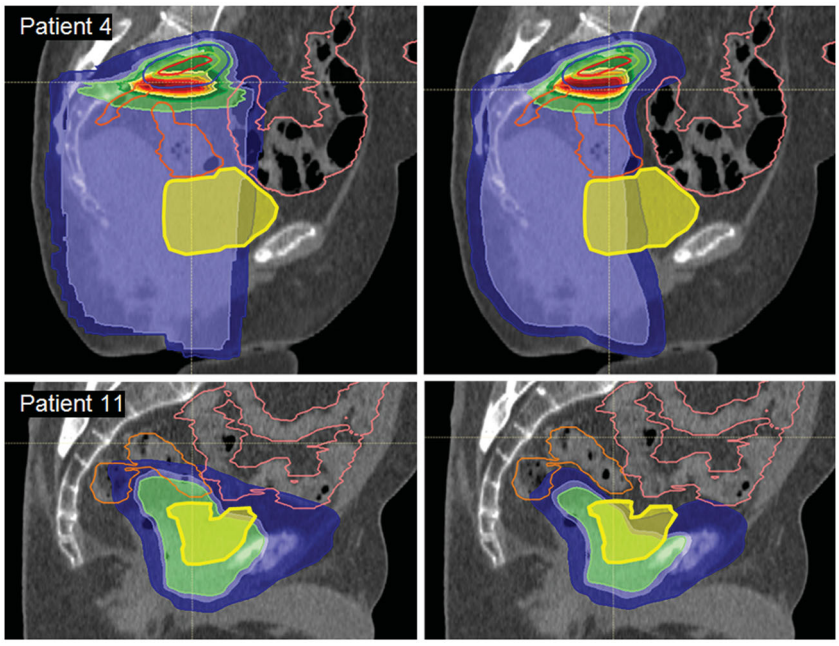

Figure 2. Impact of bladder volume reduction at reRT (yellow colour fill) on cumulative dose based on RIR (left) and DIR (right) of original dose. Patient 4: based on RIR, the cumulative dose to small bowel (salmon pink) appears higher than when the previous dose is deformed to appropriately reflect the smaller bladder and subsequent more inferior position of colon at reRT, i.e., smaller bladder 'pulls' original isodoses infero-posteriorly (small bowel $D_{10\ cm^3}$ reduced from 62.5 Gy EQD2 based on RIR to 42.9 Gy EQD2 based on DIR). Patient 11: based on RIR the cumulative dose to colon (orange) appears higher than when previous dose is deformed to appropriately reflect the smaller bladder at reRT (colon $D_{0.5\ cm^3}$ reduced from 60.6 Gy EQD2 with RIR to 50 Gy EQD2 with DIR, small bowel $D_{5\ cm^3}$ and $D_{10\ cm^3}$ also reduced in this example but dose differences of less clinical relevance ($D_{5\ cm^3}$: 35.3 Gy to 25.8 Gy and $D_{10\ cm^3}$: 30.6 Gy to 19.9 Gy; all doses EQD2).

In five cases, DIR (with EQD2 dose summation; Strategy 3) was considered to have had a clinically relevant impact on maximum doses: (i) in one case, bladder filling changes markedly reduced colon dose (Patient 11 (Figure 2): colon $D_{0.5\ cm^3}$ reduced from 60.6 Gy EQD2 with RIR (Strategy 2) to 50 Gy EQD2 with DIR (Strategy 3), i.e., moving from higher, less clinically established cumulative doses, near steep dose gradients, towards more acceptable cumulative doses); (ii) in one case, DIR increased the cumulative planned colon dose due to bowel gas (Patient 06: colon $D_{0.5\ cm^3}$ increase from 37 Gy EQD2 to 52.5 Gy EQD2; Figure 3); (iii) in one case both bladder filling and bowel gas effects were present (Patient 19 (Figure 3) overall colon $D_{0.5\ cm^3}$ reduced from 58.4 Gy EQD2 with RIR to 52.6 Gy EQD2 with DIR); (iv) in one case a reduction in bladder filling resulted in a substantial reduction in cumulative small bowel dose (Patient 17: small bowel $D_{0.5\ cm^3}$ reduced from 59.1 Gy EQD2 to 12.4 Gy EQD2), and (v) in one further case, correctly modelling a change in colon position (unrelated to bladder filling) with DIR resulted in a reduced maximum colon dose (Patient 8: colon $D_{0.5\ cm^3}$ reduced from 53.4 Gy EQD2 with RIR to 43.7 Gy EQD2 with DIR).

In a further three cases, reductions in bladder filling did not clinically impact on maximum doses but were considered to have a clinically relevant impact on the 5 and/or 10 cm^3 ($D_{5/10\ cm^3}$) threshold small bowel doses (Patient 2: $D_{5/10\ cm^3}$ reduced from 57.5/52.3 Gy to 46.3/30.0 Gy; Patient 4 (Figure 2): $D_{10\ cm^3}$ reduced from 62.5 Gy to 43.9 Gy; Patient 12: $D_{5\ cm^3}$ reduced from 51.1 Gy to 43.6 Gy; all doses EQD2). In addition, in Patient 6, the impact of correctly modelling rectal gas with DIR (as well as increasing colon $D_{0.5\ cm^3}$ as above; Figure 3) resulted in a clinically relevant increase in small bowel $D_{5\ cm^3}$ from 44.3 Gy EQD2 with RIR to 52.2 Gy EQD2 with DIR.

The anatomical effects described above were also observed to some extent in the remaining patients in the cohort, but were not clinically significant for reRT, due to the relative reRT and original RT field locations.

Of note, of the three cases mentioned above, where RIR and EQD2 dose summation (Strategy 2) resulted in maximum cumulative doses >90 Gy EQD2 in at least one OAR, based on DIR (Strategy 3), in all three, cumulative maximum doses remained high (Patient 1: small bowel $D_{0.5\ cm^3}$ 96.9 Gy with RIR and 97.7 Gy with DIR; Patient 4: small bowel $D_{0.5\ cm^3}$ 107.6 Gy with RIR and 106.4 Gy with DIR, sacral plexus $D_{0.1\ cm^3}$ 119.5 Gy with RIR and 117.8 Gy with DIR; Patient 7: bladder $D_{0.5\ cm^3}$ 110.1 Gy with RIR and 110.7 Gy with DIR; all doses EQD2).

Discussion

Isolated loco-regional relapse occurs in 5%–32% of patients who have previously received radical-intent pelvic (chemo) radiotherapy [9–13] and limited evidence suggests that re-irradiation is a promising treatment technique, potentially delaying or preventing the need for other interventions [5]. The use of re-irradiation is increasing, although approaches to re-irradiation are heterogeneous and there are no validated cumulative OAR constraints for reRT in the pelvis. Patients can experience marked anatomical and positional changes between two courses of radiotherapy and methods to take account of this, when considering cumulative doses,

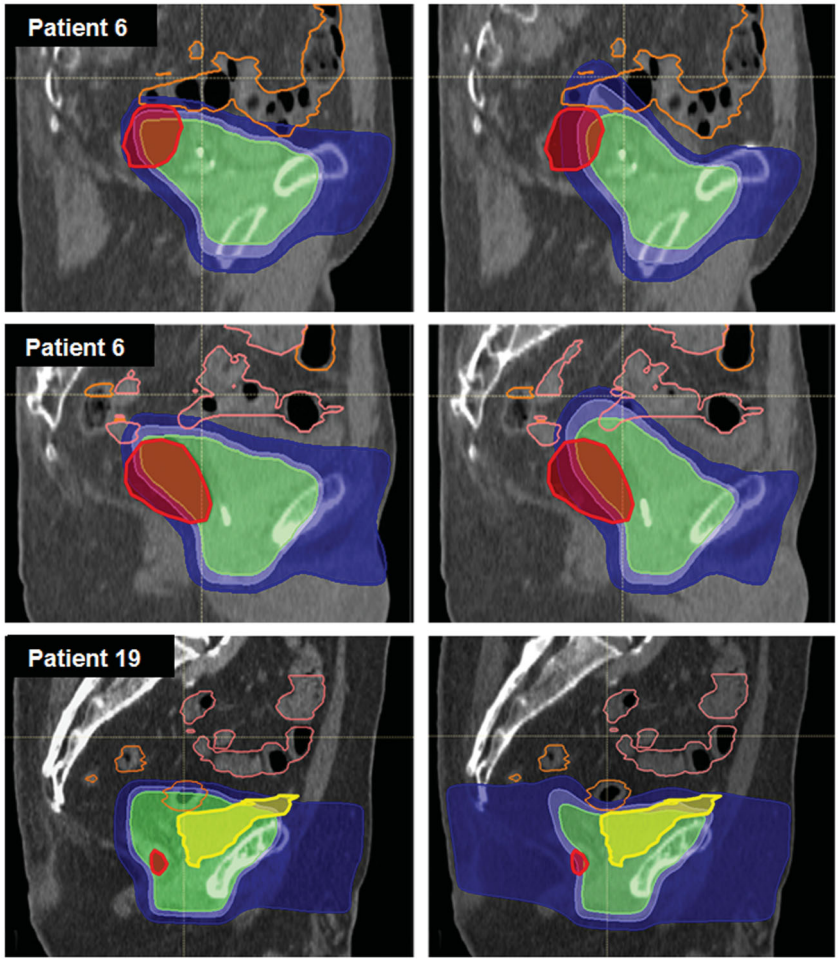

Figure 3. Impact of bowel gas (red colour fill) on cumulative dose based on RIR (left) and DIR (right) of original dose. Patient 6: based on RIR, the cumulative dose to colon (orange) and small bowel (salmon pink) appears lower than based on DIR, where bowel gas 'pushes' previously irradiated colon anteriorly and superiorly, closer to the reRT target, resulting in higher combined doses (colon $D_{0.5\ cm^3}$ increased from 37 Gy with RIR to 52.5 Gy with DIR. Small bowel D_{5cm3} increased from 44.3 Gy to 52.2 Gy; all doses EQD2). Patient 19: both bladder reduction and gas effects present: correctly modelling bowel gas 'pushes' original isodoses more superiorly near the posterior bladder, while the smaller bladder 'pulls' the more anterior isodoses more inferiorly (overall colon $D_{0.5\ cm^3}$ reduced from 58 Gy EQD2 based on RIR to 52 Gy EQD2 with DIR).

are not well established. Furthermore, treatment planning systems do not routinely take account of difference in fraction size when summating plans, instead providing summated doses based on physical dose summation. The STRIDeR project aims to facilitate more informed reRT by accounting for anatomical and positional change and incorporating radiobiology. Here we compared three approaches to dose summation for reRT, incorporating anatomical change and fraction size correction to different extents.

Methods that use physical dose summation are radiobiologically meaningless and can mask potential OAR overdose, putting the patient at risk of toxicity. Voxel-wise dose summation in EQD2 provides more meaningful dose summation, highlighting areas of higher cumulative dose, which could otherwise be 'missed'. Indeed, in this series, 14% of patients received cumulative doses in excess of 90 Gy EQD2, not identified using physical dose summation. Further useful information can be obtained by also integrating DIR into the dose accumulation pathway. Whilst there are many commercially available DIR solutions [14] the underlying algorithms fall into either image-based or contour based methods. Here we investigated both types of algorithm, separately and in combination. DIR was found to be potentially clinically important in 38% of patients. In these cases, dose differences between RIR and DIR of $\geq$6 Gy EQD2, at dose levels $\sim$50 Gy EQD2 where the risk of overlap with steep dose gradients becomes non-negligible, were observed. These were mainly due to changes in bladder and/or bowel gas between courses, and also resulting in changes in bowel position. Here our patient-specific DIR approach more appropriately deformed original dose, particularly for these mobile organs, giving a more relevant approximation of cumulative dose. Static organs (femoral heads, sacral plexus) were less affected, as would be expected for structures that are bony or situated close to bone, and so do not undergo marked deformation.

Clinical usability of our patient-specific DIR approach for reRT was validated by clinical assessment, geometric, deformation vector, and dosimetric analyses, in all 21 cases, although utility for reRT varied due to relative position of reRT PTV(s), original dose distributions, and critical OARs. DIR was, however, consistently preferred over RIR, although it was acknowledged that individual small bowel loops were often improperly registered.

Geometric analysis also demonstrated the benefit of the DIR strategy, with all metrics showing improved overlap of all major pelvic OARs. Whilst global dose summation requires robust registration across the pelvis, our SABR nodal reRT cohort predominantly received treatment near the original RT field edge and relevant DVH constraints are based on near-maximal dose. Hence, only a relatively small region around the reRT PTV is liable to significant dose overlap, reducing the requirements on DIR. However, the global accuracy of our combined strategy improves volumetric non-maximal combined DVH estimates.

Our study is limited by number of cases, the specific setting (pelvic SABR reRT) and high male/female ratio (due to prevalence of prostate cases). However, the large variation in patient anatomies, including surgery and change in patient positioning, demonstrates the range of challenges in typical clinical scenarios and the need for individualized assessment as to the best approach when considering cumulative dose. We acknowledge that DIR does not provide a 'perfect' solution, particularly for bowel loops; but the aim of this paper, was primarily to highlight the importance of considering anatomical change and the potential value of DIR over RIR in certain clinical situations, as well as underline the need for radiobiological, rather than physical, dose summation. Our series consists of patients with bone and nodal recurrences, reflecting the cohort of patients who received re-irradiation in practice. Even where reRT targets do not significantly overlap with the original treatment, cumulative doses to OARs, when considering anatomical changes and radiobiology, were shown to be of potential clinical concern. We have not dealt with more central recurrences, as these patients have not been re-irradiated in our center and data were therefore unavailable to us. In the setting of more central recurrences, issues related to changes in anatomy and OAR of most concern may differ from the cases described here, and so this patient subset would require separate evaluation.

One major challenge of pelvic re-irradiation is that the optimal cumulative OAR constraints are not well defined [5, 8]. We cannot therefore say which patients would have been definitively 'overdosed' as a result of different dose summation strategies. We have however attempted to highlight those cases where the lack of radiobiological dose summation, and/or DIR, resulted in doses that were different to those reported without these strategies and also considered of potential clinical relevance. If our understanding of cumulative normal tissue tolerance in the reRT setting is to improve, then it will be essential that strategies to address anatomical change and radiobiology are incorporated, such that scientifically meaningful cumulative doses can be correlated with clinical toxicity data.

Clinical confidence in delivering pelvic SABR reRT is currently limited by dose deformation and summation uncertainties, in a patient cohort with limited alternatives. Within a commercial treatment planning system we have demonstrated different approaches to dose accumulation and have highlighted the need for radiobiological dose summation and the clinical importance of patient-specific DIR strategies in selected cases. With a single case report previously illustrating the potential of DIR and radiobiological dose summation for pelvic reRT [15], and other groups dealing only with extra-pelvic sites [16–19], this represents a significant advance for reRT dose summation.

Conclusion

Re-irradiation cases require individualized assessment when considering dose summation with the previous treatment plan. Fractionation correction is necessary to meaningfully assess cumulative doses and reduce the risk of unintentional OAR overdose. DIR can add clinically relevant information in selected cases, especially for significant anatomical change between treatment courses. Robust solutions for cumulative dose assessment offer the potential for improved understanding of cumulative OAR tolerances.

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