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Original Article

Dose Accumulation for Pelvic Stereotactic Ablative Radiotherapy Reirradiation

F. Slevin *†[1], C. O'Hara ‡[1], J. Entwisle ‡, J. Lilley ‡, M. Nix ‡, C. Thompson ‡, M. Tyyger ‡, A.L. Appelt *‡[2], L.J. Murray *†[2]

* Leeds Institute of Medical Research, University of Leeds, Leeds, LS9 7TF, UK
† Department of Clinical Oncology, Leeds Teaching Hospitals NHS Trust, Beckett Street, Leeds, LS9 7TF, UK
‡ Department of Medical Physics, Leeds Teaching Hospitals NHS Trust, Beckett Street, Leeds, LS9 7TF, UK

Abstract

Aims: Despite the increasing use of reirradiation, our understanding of appropriate normal tissue dose constraints remains limited. This is intrinsically tied to major uncertainties concerning evaluation of cumulative doses from multiple treatment courses. This study aimed to: i) retrospectively evaluate cumulative normal tissue doses in patients treated with pelvic stereotactic ablative radiotherapy (SABR) reirradiation, taking account of anatomical change and fraction size effects, and ii) produce preliminary data regarding safe cumulative normal tissue doses.

Materials and methods: Fifty-six patients treated with pelvic SABR reirradiation for locoregional recurrence after prior radical or (neo)adjuvant radiotherapy in the pelvis were included. Original-treatment computed tomography (CT) scans were deformably registered to the reirradiation CTs; and target volumes, organs at risk (OARs), and dose distributions were transferred from the original anatomy to the reirradiation scan. Original and reirradiation dose distributions were converted into equivalent dose in 2-Gy fractions (EQD2). Cumulative doses were calculated using deformable image registration (DIR)—based dose summation and/or summed maximum doses (D0.5 cc) for each OAR. Severe toxicity events up to 2 years post reirradiation were evaluated.

Results: Most patients had prostate cancer (85.7%) and were treated for pelvic nodal recurrence (75%) with a single target volume (91.1%) using a prescription dose of 30 Gy in 5 fractions (90.3%). The median time between original and reirradiation was 53 months (interquartile range [IQR]: 36-79). Based on DIR, cumulative doses in EQD2 of up to 82.8 Gy for the rectum, 110.2 Gy for the bladder, 69.8 Gy for the colon, 101.4 Gy for the sacral plexus, and 108.1 Gy for the vessels were observed. Based on summed D0.5 cc, cumulative doses of up to 111.9 Gy were delivered to the small bowel. No severe toxicity events which could be attributed to reirradiation were observed.

Conclusions: This study has demonstrated feasibility of per-voxel anatomically and radiobiologically appropriate 3-dimensional evaluation of cumulative normal tissue doses in patients previously treated with pelvic SABR reirradiation. No toxicity events could be attributed to the cumulative or reirradiation doses delivered.

Key words: Dose accumulation; image registration; pelvic cancer; reirradiation; stereotactic ablative radiotherapy; stereotactic body radiotherapy

Introduction

Radiotherapy is an important component of the curative-intent management of multiple pelvic malignancies, including prostate, anorectal, and gynaecological cancers. Despite this, the development of a pelvic recurrence close to or within the previous radiotherapy volume is a significant clinical problem and may affect 5% to 25% of patients depending on the primary tumour type [1–6].

Reirradiation is the delivery of a further course of radiotherapy within or close to previously irradiated normal tissue [7,8]. There is increasing interest in reirradiation, driven by the potential to achieve durable local control of recurrent pelvic disease, deferral of the need to commence palliative systemic anticancer therapies,

Author for correspondence: F. Slevin, Leeds Institute of Medical Research, University of Leeds, St James's University Hospital, Beckett Street, Leeds, LS9 7TF, UK.
E-mail address: finbarslevin@nhs.net (F. Slevin).

[1] These authors contributed equally and share first authorship.
[2] These authors contributed equally and share last authorship.

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avoidance of invasive or potentially morbid surgery, and improved survival [9,10].

A key consideration for reirradiation decision-making is the potential for radiation-related toxicity where cumulative doses across the previous and reirradiation treatment courses may exceed standard normal tissue tolerance levels [8]. However, there is limited understanding concerning the most appropriate normal tissue dose tolerances in the reirradiation setting, and uncertainties exist regarding evaluation of cumulative doses across the original and reirradiation treatments. These issues have limited clinical implementation and uptake of reirradiation. There are several additional challenges to consider for reirradiation. Patients will often exhibit considerable anatomical change between treatment courses, for example, as a result of extensive surgery, and/or there may be changes in weight/body composition and the shape/position of normal organs. This makes image registration for dose mapping between treatment courses particularly challenging. Further challenges concern calculation and summation of equieffective doses, taking fraction-size effects as well as tissue recovery of previously irradiated normal tissue into account. Appropriate α/β values and tissue recovery factors are still largely unknown [11].

National Health Service (NHS) England introduced stereotactic ablative radiotherapy (SABR) for the treatment of metachronous oligometastatic disease via the Commissioning through Evaluation (CtE) programme, which has led to widespread implementation of this technique [12]. The ability to spare normal tissues using SABR because of narrow planning target volume (PTV) margins and rapid dose fall-off beyond the target is potentially attractive for reirradiation [9]. In a limited number of NHS centres, pelvic SABR reirradiation for locoregional oligorecurrent disease was permitted within this commissioning programme. To date, cumulative doses, considering the original and reirradiation normal tissue doses and with reference to toxicity outcomes, have not been reported for patients treated within the programme.

We previously developed Support Tool for Reirradiation Decisions guided by Radiobiology (STRIDeR), a tool that allows for evaluation of reirradiation cumulative doses to normal tissue in the pelvis taking anatomical change and differences in fraction size into account [13,14]. It incorporates selective use of deformable image registration (DIR) and rescaling of dose distributions into equivalent dose in 2-Gy fractions (EQD2) to enable anatomically and radiobiologically appropriate per-voxel assessment of cumulative equieffective normal tissue doses [15,16].

We here applied the STRIDeR pathway to a large cohort of patients treated at our centre with pelvic SABR reirradiation within the CtE programme. By doing so, we aimed to demonstrate the process of detailed 3-dimensional (3D) evaluation of cumulative doses using our STRIDeR tool, including correlation with clinical toxicity data, with the secondary aim of producing preliminary guidance regarding safe cumulative normal tissue constraints.

Methods

Patient Population

In this single-centre study, 56 patients, consecutively treated using pelvic SABR reirradiation for locoregional disease recurrence between 2016 and 2021 at Leeds Teaching Hospitals NHS Trust (LTHT) within the CtE programme, were retrospectively identified from an institutional database. All patients had previously received radical or (neo)adjuvant radiotherapy of at least 40-Gy EQD2 ($\alpha/\beta = 3$ Gy) as part of curative-intent management of their primary cancer. Reirradiation prescription doses were up to 30 Gy in 5 fractions. Patient selection, treatment, and follow-up were according to guidelines and standards set out in the CtE SABR programme. Follow-up was scheduled at 4 to 6 weeks post reirradiation then at 3, 6, 12, 18, and 24 months, and thereafter per standard of care (typically 6-12 monthly).

Evaluation of Cumulative Doses

Original and reirradiation treatment planning data were imported into RayStation Research 11A DTK (RaySearch Laboratories AB, Stockholm, Sweden).

Clinical organ at risk (OAR) structures were assessed for completeness and accuracy by experienced clinical oncologists, dosimetrists, and medical physicists. Contours were added or edited if necessary to ensure consistency. Delineated structures on the original and reirradiation computed tomography (CT) included the rectum, bladder, small bowel (delineated within the region of the reirradiation PTV), femoral heads, and colon. The vessels, cauda equina, and sacral plexus were delineated only on the reirradiation CT. The descending colon was also delineated on the original and reirradiation scans to aid DIR.

The original planning CT was rigidly registered to the reirradiation CT and then deformably mapped to the reirradiation anatomy. Due to differences in patient anatomy between original and reirradiation CTs (including as result of surgery and organ positional changes), the deformable registrations were complex, and, therefore, to produce realistic deformation maps, the previously developed STRIDeR registration pathway by Nix *et al.* was followed [14]. This pathway is stratified on the volume of the bladder. Relevant controlling regions of interest (ROIs) were used for each deformable registration, including bones, the descending colon, the rectum, and the bladder.

A visual inspection of all registrations was performed by experienced medical physicists to ensure no nonphysical deformations. A 5-point Likert scale was applied as part of this evaluation as a subjective indication of how well structures had been deformed within the proximity of the reirradiation PTV (which ranged from 'very poor alignment' to 'excellent alignment'). Likert assessment was accomplished by mapping deformed structures onto the original CT and visually comparing these with the original

structures. OARs considered distant to the reirradiation PTV were not included in the Likert-scale assessment (defined as an OAR which received a maximum dose [D0.1 cc] <2 Gy [physical dose] in the reirradiation plan).

The original dose was mapped to the reirradiation CT based on the deformation vector field. Both the original and reirradiation treatment dose distributions were converted from physical dose to EQD2 (for the former after mapping) initially using an α/β value of 2 Gy for the sacral plexus and 3 Gy for all other OARs. The original mapped EQD2 dose was summed with the reirradiation EQD2 dose to create a cumulative EQD2 dose distribution on the reirradiation CT. Voxels of overlapping structures were handled using calculation priority, with α/β for neural structures overriding that of other organs. No tissue recovery was assumed for the primary cumulative dose evaluation.

Given that there is uncertainty regarding the most appropriate α/β values, this process was repeated for several other α/β and tissue recovery values: α/β of 1 Gy for nerves and 2 Gy for other OARs, α/β of 3 Gy for nerves and 5 Gy for other OARs, and α/β of 2 Gy for nerves with 25% recovery assumed [7,17–21].

Dose statistics for each OAR were extracted from the treatment planning system. Calculation of dose statistics was OAR dependent. For positionally static OARs (vessels, femoral heads, and the sacral plexus), relevant dose statistics were extracted directly from the summed dose plan. For structures where a variability in the performance of deformable registration was likely (the bladder, colon, and rectum), two approaches were taken to assess the cumulative dose: i) dose statistics were extracted from the summed dose plan, as mentioned earlier, and ii) maximum (D0.5 cc) OAR doses were extracted from both original and reirradiation EQD2-transformed plans and summated. For the colon, doses were extracted only for the part of the structure within 5 cm of the reirradiation PTV. It was accepted that the maximum dose in the original and reirradiation plans may not fall in exactly the same place, but this was a conservative approach, which was appropriate where the reliability of deformable registration was uncertain. For the small bowel, deformable registration was consistently inaccurate at a loop-by-loop level. Therefore, an alternative approach was used: the reirradiation PTV was mapped onto the original CT using rigid registration and the maximum (D0.5 cc) small bowel dose within 5 cm of the mapped reirradiation PTV extracted, along with the maximum dose (D0.5 cc) to small bowel from the reirradiation. These doses were then summed to give an approximation of maximum cumulative small bowel dose in the region of the reirradiation PTV; a conservative approach, as mentioned earlier.

Toxicity Evaluation

Toxicity data which had been submitted from LTHT to the CtE programme were obtained from NHS England; however, these were incomplete for the majority of patients. Therefore, additional toxicity data were obtained by retrospective evaluation of local electronic health records at LTHT. Acute ($\leq$3 months post reirradiation) and late severe clinician-reported toxicities up to 2 years post reirradiation were evaluated. Severe toxicity was taken to represent grade 3 or greater events, as per Common Toxicity Criteria for Adverse Events (CTCAE) version 5. Toxicities were evaluated for the following domains: fatigue, gastrointestinal (GI), genitourinary (GU), musculoskeletal, and neurological. Further clinical review was performed by two experienced clinicians (FS and LJM) to determine relationships of toxicities to reirradiation (e.g., a toxicity that was recorded after reirradiation but that was also present at the same or greater severity before reirradiation was not considered to represent a reirradiation toxicity).

Results

Patient Population

Patient characteristics are summarised in Table 1. A majority of patients had a primary diagnosis of prostate cancer (85.7%) and were treated using SABR reirradiation for pelvic nodal recurrence (75%) with a single target volume (91.1%) using a prescription dose of 30 Gy in 5 fractions. The median time between original and reirradiation treatments was 53 months (IQR 36–79).

Deformable Image Registration

Image registration results were excellent or good for the majority of bladder (98%), rectum (92%), sacral plexus (98%), and femoral head (100%) structures; with less reliable results for vessels (64%) and colon (62%). See Supplementary Table 1 for full details.

Evaluation of Cumulative Doses

A summary of cumulative doses to each OAR is provided in Table 2, and the range of doses is illustrated in Figure 1. Based on DIR, cumulative doses in EQD2 of up to 82.8 Gy for the rectum, 110.2 Gy for the bladder, 69.8 Gy for the colon, 101.4 Gy for the sacral plexus, and 108.1 Gy for the vessels were observed. Based on maximum dose (D0.5 cc) summation, cumulative doses in EQD2 of up to 92.4 Gy for the rectum, 111.9 Gy for the bladder, 94.3 Gy for the colon, and 111.9 Gy for the small bowel were observed.

Table 2 also shows the difference in cumulative doses to OARs using DIR-based dose summation versus sum of D0.5 cc values across the original and reirradiation treatments. Median cumulative doses in EQD2 appeared smaller for the rectum (61.4 versus 64.9 Gy), bladder (62.4 versus 65 Gy), and colon (45 versus 45.6 Gy) using DIR-based versus sum of D0.5 cc approaches, respectively.

Most patients received cumulative doses to OARs below 80 Gy, as illustrated in Figure 3. Based on DIR, two patients received a cumulative D0.5 cc over 80 Gy to the bladder (86.0 Gy and 110.2 Gy); one patient received a cumulative D0.5 cc over 80 Gy to the rectum (82.8 Gy); two patients received a cumulative D0.5 cc over 80 Gy to the small bowel

Table 1
Patient characteristics

Characteristic	Number of patients (%) or median (IQR)
Age at original treatment (years)	65 (59-70)
Age at reirradiation (years)	70 (65-74)
Sex	
Female	4 (7.1%)
Male	52 (92.9%)
Diagnosis	
Prostate cancer	48 (85.7%)
Rectal cancer	7 (12.5%)
Anal cancer	1 (1.8%)
Original dose-fractionation schedule	
72-74 Gy in 36-37 fractions	12 (21.4%)
54-66 Gy in 30-33 fractions	6 (10.7%)
50-60 Gy in 20 fractions	24 (42.9%)
45-50.4 Gy in 25-28 fractions	5 (8.9%)
35.75-37.5 Gy in 13-15 fractions	7 (12.5%)
25 Gy in 5 fractions	2 (3.6%)
Time interval between original and reirradiation (months)	53 (36-79)
Reirradiation site	
Pelvic node	42 (75%)
Nonsacral pelvic bone	10 (17.9%)
Sacrum	4 (7.1%)
Reirradiation dose-fractionation schedule[a]	
30 Gy in 3 fractions	4
30 Gy in 5 fractions	56
25 Gy in 5 fractions	2
Number of target volumes	
1	51 (91.1%)
2	4 (7.1%)
3	1 (1.8%)
Reirradiation GTV(s) (cm^3)	2.75 (1.14-8.28)

[a] Numbers represent individual lesions and therefore add up to more than the total patient number. GTV, gross tumour volume; IQR, interquartile range.

(85.1 Gy and 90.2 Gy); and one patient received a cumulative D0.5 cc over 80 Gy to the sacral plexus (101.4 Gy). Doses to the vessels were slightly higher, with three patients receiving a cumulative D0.5 cc over 90 Gy to the vessels (98.5 Gy, 103.0 Gy, and 108.1 Gy).

The relative contribution to cumulative maximum doses from the original and reirradiation treatments varied per OAR, as is shown in Figure 2. For the rectum and bladder, the cumulative dose was primarily driven by the original treatment, whereas the majority of small bowel cumulative dose was delivered during the reirradiation. There was considerable variation across the cohort in terms of overlap between OARs and reirradiation target volumes, as illustrated in Figure 4.

Toxicity Outcomes

Median follow-up duration was 61 months (95% confidence interval [CI]: 42.3-79.8). Complete follow-up information for the 2-year toxicity assessment period was available for the majority of participants (78.6%), but only minimal follow-up information could be obtained for 12 participants (21.4%) who lived out of area and returned to their local centre post reirradiation. Four severe GU/GI events which required intervention were observed up to 2 years post reirradiation. Further clinical review established that none of these were attributable to the reirradiation treatment (see Table 3).

Discussion

This study builds on our prior work in per-voxel anatomically and radiobiologically appropriate 3D evaluation of cumulative normal tissue doses using our STRIDeR tool and has demonstrated the feasibility of applying this methodology in patients previously treated with pelvic SABR reirradiation [13,14,22]. To our knowledge, this is the largest published series reporting cumulative doses for patients treated with pelvic SABR reirradiation. In contrast to the heterogeneity often present within reirradiation series, a strength of this study is that patients were treated using a consistent approach [9]. The majority of patients were treated for pelvic nodal recurrent prostate cancer using a reirradiation of 30 Gy in 5 fractions to a single target volume. Encouragingly, no severe late toxicity was observed that could be attributed to the reirradiation, even with cumulative doses reaching 82.8 Gy, 110.2 Gy, 69.8 Gy, 111.9 Gy,

Table 2
Summary of doses to each OAR calculated using DIR-based dose summation and/or the sum of maximum D0.5 cc, using a range of α/β values with/without incorporation of a recovery factor from the original treatment

OAR		Median dose in EQD2 (Gy) (IQR)			
		α/β = 3 Gy (2 Gy for the sacral plexus)	α/β = 2 Gy (1 Gy for the sacral plexus)	α/β = 5 Gy (3 Gy for the sacral plexus)	α/β = 2 Gy for the sacral plexus with 25% recovery
Bladder (D0.5 cc)	DIR-based dose summation	62.4 (60-71.7)	63.5 (61.7-72.9)	60.6 (58-71.1)	
	Sum of maximum D0.5 cc	65.0 (60.4-73.8)	66.2 (62.1-73.8)	63.2 (58.4-73.0)	
Colon (D0.5 cc)	DIR-based dose summation	45.0 (21.0-57.4)	47.5 (22.0-58.7)	43.8 (20.3-56.2)	
	Sum of maximum D0.5 cc	45.6 (21.0-67.1)	46.4 (21.1-68.2)	45.5 (21.7-64.0)	
Rectum (D0.5 cc)	DIR-based dose summation	61.4 (59.0-68.1)	63.2 (60.5-68.7)	59.5 (57.3-68.3)	
	Sum of maximum D0.5 cc	64.9 (59.6-71.0)	65.7 (61.0-71.4)	63.1 (57.9-70.7)	
Small bowel (D0.5 cc)	Sum of maximum D0.5 cc	22.2 (10.3-54.1)	22.8 (10.2-59.3)	21.1 (10.4-47.9)	
Sacral plexus (D0.1 cc)		48.5 (34.9-60.9)	49.5 (32.3-66.9)	47.1 (33.9-58.3)	41.9 (28.1-52.9)
Vessels (D0.5 cc)		60.3 (46.0-65.5)	67.0 (50.1-72.9)	52.8 (43.6-58.7)	
Left femoral head (D10 cc)		32.6 (24.6-38.6)	31.7 (23.8-38.2)	33.4 (25.0-39.8)	
Right femoral head (D10 cc)		33.7 (23.4-40.5)	33.0 (22.5-40.3)	34.1 (24.5-40.7)	

D0.5 cc, maximum dose to 0.5 cc; DIR, deformable image registration; EQD2, equivalent dose in 2-Gy fractions; IQR, interquartile range; OAR, organ at risk.

and 101.4 Gy for the rectum, bladder, colon, small bowel, and sacral plexus, respectively. This may provide preliminary evidence of 'safe' cumulative doses for pelvic reirradiation, although only a very small number of patients received over 80 Gy cumulative EQD2 to OARs meaning that higher doses were driven by relatively small numbers of patients. This may explain why no severe late toxicity events were observed.

No clear standard exists regarding image registration for reirradiation dose accumulation. In previously published studies, dose summation strategies used either rigid registration of original and reirradiation radiotherapy imaging and dose or side-by-side comparison [23–29]. There are limited published data concerning equieffective dose accumulation using DIR. Cao *et al.* evaluated 40 patients who received SABR reirradiation for locally recurrent pancreatic cancer and evaluated the correlation between cumulative dose to the stomach, duodenum, and small bowel and moderate or worse GI toxicity events [30]. The authors identified that the volume receiving 10 Gy (V10) for the stomach and mean dose (Dmean) to the small bowel may be predictive of moderate or worse GI toxicity. In our series, we did not identify severe toxicities to permit a corresponding analysis. While the toxicity thresholds for cumulative OAR doses are not well understood, it is possible that these are lower for the stomach, duodenum, and proximal small bowel than for pelvic OARs [31,32].

There was variability per OAR in the relative contribution in dose from original and reirradiation plans to the cumulative maximum dose point. The rectum and bladder typically demonstrated greater contribution from the original treatment plans. This may reflect proximity of the rectum to the prostate gland/prostatic fossa and because patients were typically treated with an empty bladder for reirradiation. In contrast, the reirradiation contribution was greater for the small bowel, which may reflect the location of pelvic nodal recurrences as well as the bladder filling strategies typically used in primary anorectal and prostate radiotherapy [33]. For the rectum, bladder, and colon, DIR-based dose summation appeared to result in lower cumulative doses than a sum of D0.5 cc, although the absolute differences in cumulative doses was <5 Gy. In theory, DIR-based dose summation may permit less conservative approaches to dose summation which may avoid unnecessary compromise of target volume coverage, accepting, as highlighted later in text, that there are limitations to anatomical deformation using DIR [14,34]. In clinical practice, the differences between the full DIR-based approach and a more conservative summation of near–max dose metrics may be sufficiently small to not offset the added complexity involved in a DIR-based approach.

Despite increasing interest and clinical use of pelvic reirradiation, several uncertainties remain which need to be addressed [7,8]. These include the most appropriate minimum time interval between radiotherapy courses, as well as the optimum radiotherapy technique(s), dose fractionation schedules, and image registration practices. No validated cumulative OAR constraints exist for reirradiation, with these often guided by expert consensus [35]. Different approaches are taken to dose constraints for reirradiation, including the use of traditional OAR constraints cumulatively, with/without incorporation of recovery factors

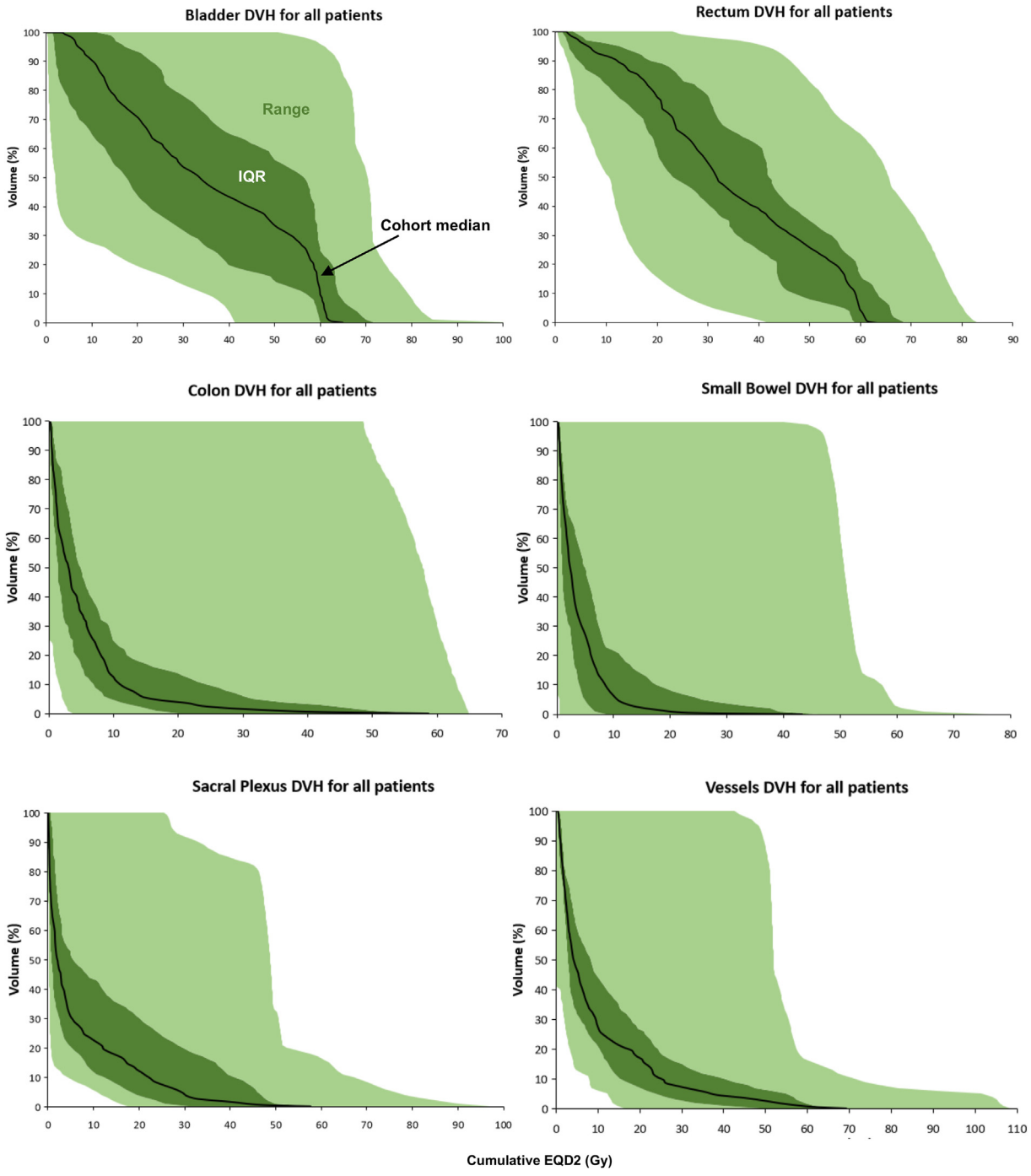

Fig 1. Dose volume histograms illustrating the variation in cumulative doses in EQD2 to each OAR across the cohort, using $\alpha/\beta = 2$ Gy for nerves and 3 Gy for all other OARs (based on dose mapping with deformable registration). In each subfigure, the black line represents the median dose, dark green represents the interquartile range (IQR), and light green represents the range.
DVH, dose volume histogram; EQD2, equivalent dose in 2-Gy fractions; IQR, interquartile range. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

depending on the time interval from the prior irradiation, or the application of cumulative maximum constraints [23,24,27–29,36]. The optimum application of recovery factors and the most appropriate α/β values within dose summation calculations is also unclear. As mentioned earlier, we have presented cumulative OAR doses based on a consistent methodology and we consider it to be reassuring that such doses did not appear to result in any severe toxicity. Table 4 shows a comparison between cumulative doses to OARs in this study and previously published cumulative constraints [23,27–29,36,37]. Our results are broadly consistent with previously published series which described comparable cumulative doses for the bladder, colon/rectum/sigmoid colon, and small bowel associated

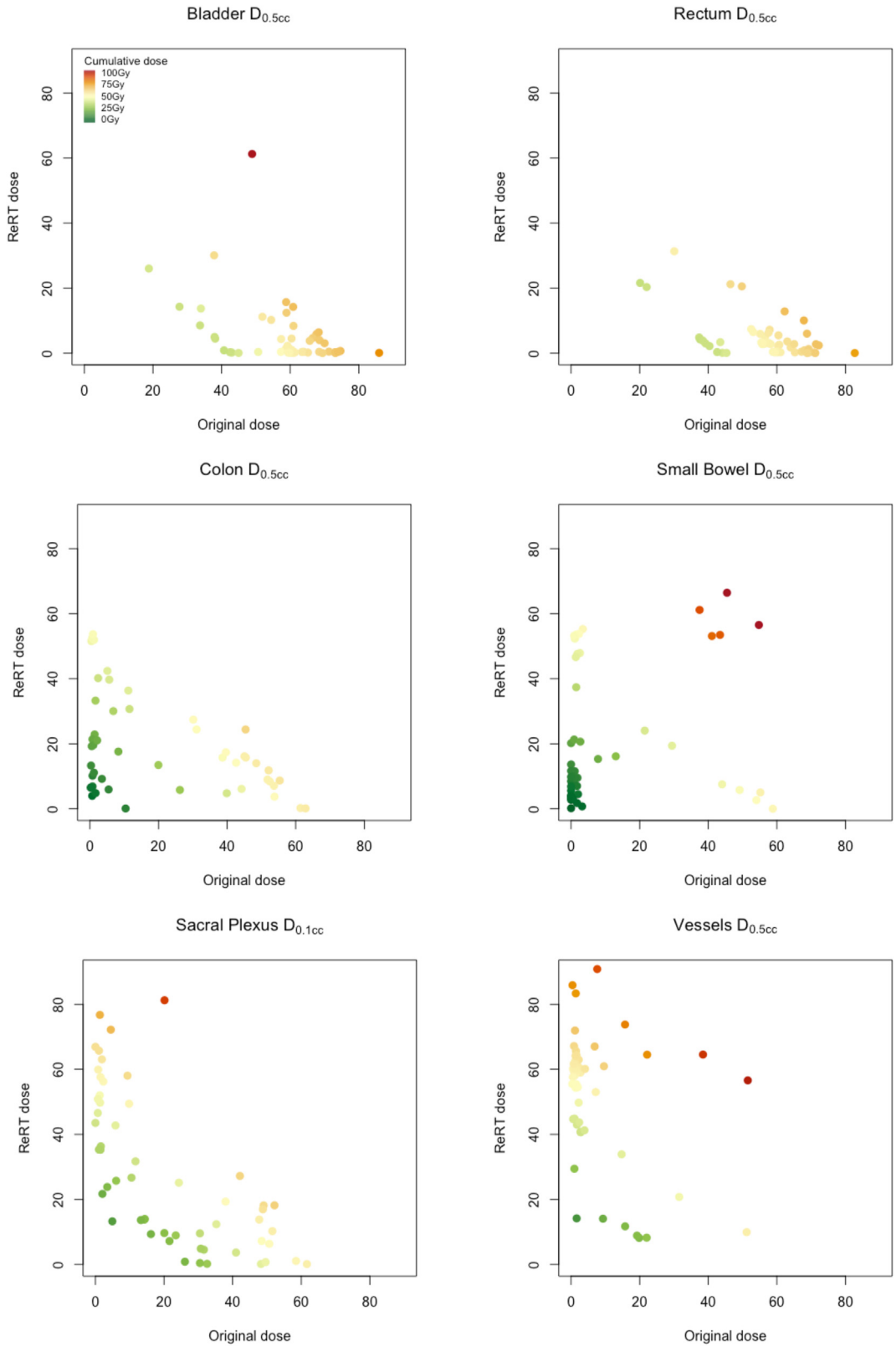

Fig 2. Scatter plots of cumulative maximum radiation doses to each OAR in EQD2, using $\alpha/\beta = 2$ Gy for the sacral plexus and 3 Gy for other OARs. These plots illustrate the relative dose contribution from the original and reirradiation treatments at the point of cumulative maximum dose. DIR-based dose summation was used for all OARs, except for the small bowel.
D0.5 cc, maximum dose to 0.5 cc; DIR, deformable image registration; EQD2, equivalent dose in 2-Gy fractions; OAR, organ at risk; ReRT, reirradiation.

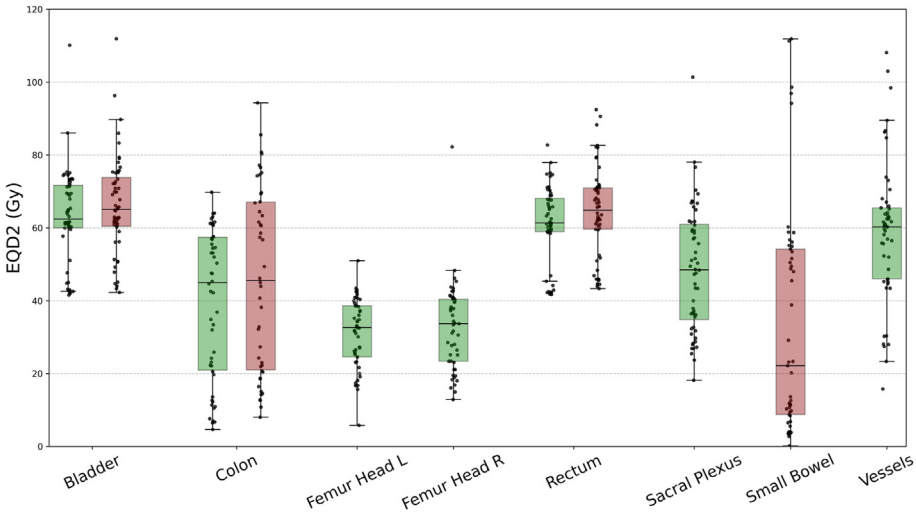

Fig 3. Box and whisker plots showing the distribution of cumulative doses for each OAR using DIR-based dose summation (green) and sum of maximum doses (red). In each plot, the central black line represents the median dose; the box corresponds to the upper and lower quartiles and the whiskers to the maximum and minimum values, unless greater than 1.5 times than the interquartile range in which case they are plotted as outlying values.
DIR, deformable image registration; EQD2, equivalent dose in 2-Gy fractions; OAR, organ at risk. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with minimal or no severe toxicity [23,27,28]. For most patients, the sacral plexus cumulative doses we observed were comparable to either those in previously published series or where a traditional constraint is used with incorporation of a recovery factor from the original irradiation [28,36]. Cumulative doses for vessels for all patients were less than a previously published constraint for aortic reirradiation, presuming the tolerance for the aorta and pelvic major vessels is similar [38].

This study has several limitations. We did not utilise DIR-based dose summation for the small bowel as it is recognised that deformation techniques are currently unreliable for this OAR [14]. More data are needed to determine the impact of our STRIDeR approach in patients with non-prostate cancer pelvic recurrence and/or multiple target volumes, although our approach did appear to work for the small number of patients in these categories in the current study. The degree of overlap between the original and reirradiation target volumes was variable throughout the cohort. While reflective of the heterogeneity commonly seen in pelvic reirradiation cases, we acknowledge that this current series contained a relatively small proportion of patients with high dose overlap for OARs. We did not account for potential random errors in patient set-up or internal organ motion across original and reirradiation treatments, which could result in differences between

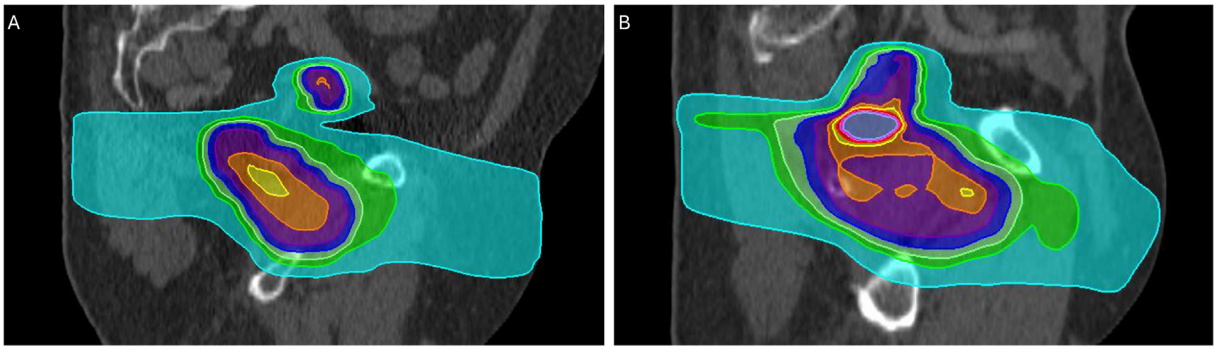

Fig 4. Two example cases of pelvic SABR reirradiation are shown, illustrating the variability in overlap between the original and reirradiation treatment volumes. Isodoses correspond to the cumulative dose in EQD2 and are visualised on the reirradiation CT, per the accompanying key. In section A, a sagittal CT slice for a patient treated with pelvic SABR reirradiation for a pelvic nodal recurrence after previous prostate radiotherapy is shown. In this example, there is low-dose overlap at the 25% isodose between the original treatment volume (inferior, 74 Gy in 37 fractions) and the reirradiation treatment volume (superior, 30 Gy in 5 fractions). In B, a sagittal CT slice for a patient treated with pelvic SABR reirradiation for a pelvic nodal recurrence after previous prostatic fossa radiotherapy is shown. In this example, there is higher-dose overlap at the 70% isodose between the original treatment volume (inferior, 66 Gy in 33 fractions) and the reirradiation treatment volume (superior, 30 Gy in 5 fractions).
CT, computed tomography; EQD2, equivalent dose in 2-Gy fractions; SABR, stereotactic ablative radiotherapy.

Table 3
Summary of severe genitourinary and gastrointestinal events and attribution

Primary tumour site	Site of SABR reirradiation	Toxicity	Management	Attribution	Maximum dose (D0.1 cc) in EQD2 to OAR from pelvic SABR reirradiation
Prostate cancer	Right external iliac node	Urinary obstruction/ radiation cystitis	TURP and ISC	HDR brachytherapy reirradiation for local recurrence	0.3 Gy at bladder base
Prostate cancer	Left common iliac, left external iliac, and right obturator nodes	Urinary incontinence	Urethral catheterisation, consideration for artificial urinary sphincter	Previous radical prostatectomy (symptoms predated SABR)	0.4 Gy to bladder
Rectal cancer	Common iliac node	Hydroureteronephrosis and small bowel obstruction	Ureteric stent	Disease progression	N/A[a]
Prostate cancer	Left obturator node	Prolapsed haemorrhoid	EUA and banding	Unrelated to SABR reirradiation	<0.1 Gy at anal canal

D0.1 cc, maximum dose to 0.1 cc; EQD2, equivalent dose in 2-Gy fractions; EUA, examination under anaesthesia; HDR, high dose rate; ISC, intermittent self-catheterisation; OAR, organ at risk; SABR, stereotactic ablative radiotherapy; TURP, transurethral resection of the prostate.

[a] Left hydroureteronephrosis and small bowel obstruction secondary to development of a new left common iliac node after SABR reirradiation.

Table 4
Summary of published OAR constraints: cumulative dose in EQD2 to 0.1 cc for each OAR is shown

Traditional constraint used cumulatively						
OAR	AAPM[a] [37]	Paradis[a] [36]	Abusaris	Smith	Li	Yoshida
Bladder	80 Gy	85 Gy	-	-	-	-
Colon/rectum/ sigmoid colon	80 Gy	70 Gy	-	-	-	-
Sacral plexus	67 Gy	70 Gy	-	-	-	-
Small bowel	70 Gy	54 Gy	-	-	-	-
Cumulative constraint and/or incorporation of recovery into traditional constraint						
OAR	AAPM[a f] (50% recovery after 12 months) [37]	Paradis[a e] (50% recovery after 12 months) [36]	Abusaris[a c d] [23]	Smith[a c d] [28]	Li[a c d] [27]	Yoshida[a b c d] [29]
Bladder	102.2 Gy	106.6 Gy	120 Gy	120 Gy	95 Gy	
Colon/rectum/ sigmoid colon	102.2 Gy	91.5 Gy	110 Gy	110 Gy	95 Gy	120 Gy
Sacral plexus	88.6 Gy	91.5 Gy	-	74.4 Gy	-	-
Small bowel	91.6 Gy	64.8 Gy	110 Gy	98 Gy	95 Gy	120 Gy

AAPM, American Association of Physicists in Medicine; EQD2, equivalent dose in 2-Gy fractions; OAR, organ at risk.
[a] α/β ratio for all OARs of 3 used except for sacral plexus (α/β of 2) and Paradis et al. (α/β of 2.5).
[b] Cumulative doses in EQD2 calculated to 1 cc instead of 0.1 cc.
[c] Larger cumulative constraints used in the studies by Abusaris et al., Smith et al., Li et al., and Yoshida et al. for the bladder, colon/rectum/sigmoid colon, and small bowel, with no additional recovery permitted.
[d] No grade 3+ toxicity reported in the study by Abusaris et al. after a median follow-up duration of 15 months (range: 2-52 months; n = 27 patients). One patient (3%) experienced grade 3 pain, but no other grade 3+ toxicity was reported in the study by Smith et al. after a median follow-up duration of 24.5 months (IQR: 17.8-28.8 months; n = 30 patients). No grade 3+ toxicity was reported in the study by Li et al. after a median follow-up duration of 33.5 months (n = 22). Four patients (12.1%) experienced grade 3 bowel toxicity in the study by Yoshida et al. after a median follow-up duration of 18 months (range: 2-156 months; n = 33).
[e] Fifty percent recovery for all OARs in Paradis et al. except for small bowel (25% recovery).
[f] Recovery not specified by the AAPM but included as illustrative of practice.

planned and delivered cumulative doses to OARs. Such variation could be significant SABR reirradiation, given the small number of fractions, and could be further investigated by comparing OAR dose accumulation across planning and on-treatment image sets. Although no obvious severe toxicity was observed, complete follow-up information was not available for all participants and this is a single-centre study, and inherent limitations in the primarily retrospective evaluation of toxicity mean that prospectively collected, multicentre data are needed to address the uncertainties which remain for pelvic reirradiation. Ongoing initiatives, including the European Organisation for the Research and Treatment of Cancer (EORTC) and European Society for Radiotherapy and Oncology (ESTRO) ReCare registry study, the recently established Reirradiation Collaborative Group (ReCOG), the UK SABR Consortium Pelvic SABR Reirradiation Guidelines and National Audit, and the EMBRACE consortium's RetroCOSMOS study should help to address these challenges [39–42].

Conclusion

This study has demonstrated feasibility of per-voxel anatomically and radiobiologically appropriate 3D evaluation of cumulative normal tissue doses in patients previously treated with pelvic SABR reirradiation. No severe toxicity events were observed which could be attributed to cumulative or reirradiation OAR doses.

Ethics

This study received ethical approval from National Health Service (NHS) Health Research Authority Yorkshire & The Humber- Bradford Leeds Research Ethics Committee on 21/03/2022 (REC reference 22/YH/0064).

Author Contribution

1. Guarantor of integrity of the entire study: AA and LM.
2. Study concepts and design: FS, COH, JE, AA, and LM.
3. Literature research: FS, COH, JE, AA, and LM.
4. Clinical studies: N/A.
5. Experimental studies/data analysis: FS, COH, JE, AA, and LM.
6. Statistical analysis: FS, COH, JE, AA, and LM.
7. Manuscript preparation: FS, COH, JE, AA, and LM.
8. Manuscript editing: FS, COH, JE, JL, MN, CT, MT, AA, and LM.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christopher O'Hara, Jonathan Entwisle, John Lilley, Ane L Appelt, and Louise J Murray report financial support was provided by Cancer Research UK. Leeds Teaching Hospitals NHS Trust has a research collaboration agreement with RaySearch Laboratories, which includes access to research software versions of RayStation treatment planning system.

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Finbar Slevin is a Clinical Trial Fellow funded by Cancer Research UK (award number 125713).

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Appendix A. Supplementary data

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