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Treatment plan optimisation for reirradiation

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Short title: Treatment plan optimisation for reirradiation

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- The STRIDeR (**S**upport **T**ool for **R**e-**I**rradiation **De**cisions guided by **R**adiobiology) pathway uses background dose to guide radiobiologically meaningful, anatomically-appropriate re-irradiation treatment planning within a commercial treatment planning system

- Uniquely, the pathway can optimise voxel by voxel in equivalent dose in 2Gy fractions (EQD2)

- The EQD2 optimisation was used to produce re-irradiation treatment plans to illustrate the use of the STRIDeR pathway

- A selective approach to deformable image registration was employed to take account of anatomical change between treatment courses

- The development of scientifically-driven and standardised strategies such as the STRIDeR pathway, to improve and learn from re-irradiation, is essential to optimise the therapeutic ratio for future patients

Treatment plan optimisation for reirradiation

Abstract

Background: The STRIDeR (Support Tool for Re-Irradiation Decisions guided by Radiobiology) project aims to create a clinically viable re-irradiation planning pathway within a commercial treatment planning system (TPS). Such a pathway should account for previously delivered dose, voxel-by-voxel, taking fractionation effects, tissue recovery and anatomical changes into account. This work presents the workflow and technical solutions in the STRIDeR pathway.

Methods: The pathway was implemented in RayStation (version 9B DTK) to allow an original dose distribution to be used as background dose to guide optimisation of re-irradiation plans. Organ at risk (OAR) planning objectives in equivalent dose in 2Gy fractions (EQD2) were applied cumulatively across the original and re-irradiation treatments, with optimisation of the re-irradiation plan performed voxel-by-voxel in EQD2. Different approaches to image registration were employed to account for anatomical change. Data from 21 patients who received pelvic Stereotactic Ablative Radiotherapy (SABR) re-irradiation were used to illustrate the use of the STRIDeR workflow. STRIDeR plans were compared to those produced using a standard manual method.

Results: The STRIDeR pathway resulted in clinically acceptable plans in 20/21 cases. Compared to plans produced using the laborious manual method, less constraint relaxation was required or higher re-irradiation doses could be prescribed in 3/21.

Conclusion: The STRIDeR pathway used background dose to guide radiobiologically meaningful, anatomically-appropriate re-irradiation treatment planning within a commercial TPS. This provides a standardised and transparent approach, offering more informed re-irradiation and improved cumulative OAR dose evaluation.

Introduction

Re-irradiation may be used in patients who develop an isolated localised recurrence in an anatomical region previously irradiated to high dose. Traditionally, re-irradiation has been approached with caution given uncertainties about normal tissue tolerance to re-irradiation. Previously, hyper-fractionation has been used to reduce the risk of late side effects[1,2]. More recently, with the advent of highly conformal techniques, and particularly for smaller volume recurrences, there has been interest in Stereotactic Ablative Radiotherapy (SABR) re-irradiation, which has the potential advantages of dose escalation within the target and rapid dose fall-off in surrounding (previously irradiated) normal tissues[3-5].

Despite recent increased uptake of re-irradiation, high quality prospective data supporting optimal use are lacking[6]. Few definitive guidelines exist[4,7] and while there have been attempts to reach consensus regarding re-irradiation, agreement across all areas is lacking[8,9]. These issues might relate to the many uncertainties and technical challenges associated with re-irradiation, including how to: i) account for anatomical change between former and re-irradiation treatments and ii) incorporate correction for fraction size effects and tissue recovery when evaluating cumulative doses from two treatment courses. The former is a particular issue for pelvic re-irradiation, where patients may have undergone surgery, experienced weight changes, or have differences in bladder filling between two radiotherapy courses. The latter applies across all sites as treatment planning systems (TPS) standardly produce dose distributions in physical dose, which cannot be meaningfully summed without taking fraction size effects into account, a functionality not routinely available in clinical TPSs. Accepting these challenges, the need for a standardised, scientifically rigorous approach to re-irradiation has been highlighted[10].

Considering the above, a re-irradiation treatment planning pathway would ideally permit:

- Use of the full original dose distribution as background dose to guide re-irradiation optimisation;
- Representation of the above in equivalent dose in 2Gy fractions (EQD2) or biologically equivalent dose (BED); to allow
- Optimisation at the voxel-by-voxel level, in EQD2 (or BED), so the process is radiobiologically meaningful;
- Use of deformable image registration (DIR), where appropriate, to take account of anatomical change between two radiotherapy courses;
- A process for DIR quality assurance, with an alternative strategy available where DIR is considered unreliable;
- The option to incorporate normal tissue recovery and variation in α/β values;
- Representation of the final plan in EQD2 and in the number of fractions for re-irradiation delivery, with capability to view this in isolation and summated with the original plan;
- Automation as far as possible but with manual input points to determine where deviation from the originally intended approach is required (e.g., in terms of DIR assessment, recovery and α/β values).

The STRIDeR project (**S**upport **T**ool for **R**e-**I**rradiation **De**cisions guided by **R**adiobiology) aims to improve re-irradiation treatment planning, by implementing the requirements above

within a commercial TPS. The first part of the project demonstrated the value of DIR, fraction size correction, and per voxel dose summation in EQD2 for cumulative dose assessment for original and re-irradiation treatment plans, compared to dose summation based on rigid image registration (RIR) and physical dose[7,11]. The second part, presented here, aims to create a pathway that uses the original radiotherapy dose distribution, corrected for anatomy and fraction size (and, optionally, tissue recovery), as background dose for re-irradiation plan optimisation. As above, for the pathway to be radiobiologically meaningful, optimisation on the combined dose distributions must be performed in biologically equieffective dose (this project utilised EQD2). This capability is not generally implemented within a commercial TPS. The work has therefore been performed in collaboration with RaySearch Laboratories AB (Stockholm, Sweden), who implemented an EQD2 optimisation process within RayStation and around which the STRIDeR pathway has been developed. We hereby present the STRIDeR pathway and illustrate its use as a standardised, scientifically-driven approach for re-irradiation treatment planning. Such a pathway promotes transparency and accountability in re-irradiation decision making, in what is often a complex and heterogeneous situation, where many 'unknowns' remain.

Methods:

Work was performed using a research version of RayStation, 9B DTK.

STRIDeR re-irradiation planning pathway

The pathway is summarised in Figure 1 and includes:

1. *Image registration with organ-specific quality assessment*

Both RIR and DIR of the original planning CT to the re-irradiation planning CT are supported. As our initial focus was pelvic re-irradiation, where anatomical change can be dramatic, a DIR approach was the preferred starting point (methodology provided elsewhere[7,12]).

As the image registration is used to guide subsequent dose mapping and plan optimisation (see below), the registration reliability must be considered, as this can vary depending on the degree of anatomical change and performance of the DIR algorithm. An organ-specific strategy that allows for varying reliance on the DIR was therefore implemented. All OARs were assigned to one of three categories:

1. Structures with DIR of consistently high quality.
2. Structures with consistently unreliable DIR.
3. Structures with variable DIR quality across patients. Where these were positioned close to the re-irradiation PTV, the DIR was assessed by an experienced clinician, to determine if the DIR was of sufficient quality to rely on dose mapping based on the image deformation vector field. Factors considered here included plausibility of the physical deformation, quality specifically around the re-irradiation PTV and potential dosimetric significance of DIR uncertainty. Where OARs were positioned further from

the re-irradiation PTV, these were excluded from the optimisation process. Given the rapid dose fall off associated with SABR, a cut-off of 5 cm was used to determine whether OARs were considered 'close to' or 'further from' the re-irradiation PTV.

For this study, we considered:

- Category 1: Less mobile structures (vessels, sacral plexus, cauda equina and bones),
- Category 2: Bowel on a loop-to-loop level,
- Category 3: Bladder and rectum.

Simplified assessment strategies may be viable for other locations, where anatomical change is less marked.

2. Dose mapping

Based on the deformation vector field, the original dose distribution was mapped to the re-irradiation dataset. For category 1 OAR in all cases, and for category 3 OAR where the DIR was considered reliable, the mapped doses were used as background dose in the optimisation process (below). For category 2 OAR in all cases, and category 3 OAR where the DIR was considered unreliable, we took a conservative approach: to guide the optimisation, we used the maximum dose originally received by the portion of OAR in closest proximity to the location of the re-irradiation target (i.e. that portion of OAR considered most relevant for, and most at risk from, re-irradiation; see Supplementary Material section S2).

3. Radiobiological optimisation using original dose as background

RayStation was adapted for biological optimisation of re-irradiation. The prototype objective functions that act on EQD2 instead of physical dose directly were extended to include recovery between treatment courses[13] and modified to be used in combination with the 'background dose optimisation' functionality. The original dose distribution mapped to the re-irradiation data set could thus be accounted for in the EQD2 calculation during optimisation.

During the optimisation process, where the DIR and subsequent dose mapping for OARs were considered reliable for use as background dose, OAR planning objectives were applied cumulatively in EQD2, i.e., across the original and re-irradiation dose distributions. In situations where the background dose exceeded the cumulative constraint, some manual adjustment of the plan optimisation was required, to avoid negatively affecting re-irradiation plan quality.

Target objectives were applied in physical dose and applied to the re-irradiation dose distribution only. Similarly, dose fall-off objectives were applied only to the re-irradiation dose distribution (Figure 2).

Where the DIR in the vicinity of the OAR and subsequent dose mapping were considered unreliable (category 2 and some category 3 OAR), the maximum dose received by each OAR from the original radiotherapy (converted to EQD2) was subtracted from the cumulative

constraint (also in EQD2) and the 'dose remaining' (converted to the number of fractions in which re-irradiation would be delivered) was used to determine the objective to guide optimisation across the entire OAR (see Supplementary Material S2 for equations used). Such objectives were, therefore, in physical dose and applied to the re-irradiation dose distribution only (Figure 2).

The constraints used here to illustrate the pathway were mainly near point or small volume maxima. As such, where the original dose distribution was used as background dose, this guided the optimiser to place dose appropriately within an OAR. For example, a high dose received by the inferior rectum during the original radiotherapy would not negatively influence the delivery of a high dose to the superior rectum during re-irradiation, when the superior rectum had not been irradiated to such a high dose originally.

OAR dose optimisation was performed using Max EUD (Equivalent Uniform Dose; parameter a=150) objectives. The objective window displays the achieved max EUD during optimisation, allowing the planner to interact live (Figure 2). All types of optimisation objectives, however, can be directly used with the cumulative EQD2 evaluation.

4. *Pathway options*

The following parameters are flexible:

- Number of previous fractions
- Number of fractions for re-irradiation
- α/β for each optimisation objective
- Amount (%) of recovery assigned to each OAR

5. *Plan evaluation*

The optimised re-irradiation plan can be viewed alone or as a cumulative dose distribution with the original plan. Cumulative dose distributions can be viewed in EQD2 (with separate α/β for each structure, i.e. specified on a per-voxel basis) or transformed to the number of fractions in which re-irradiation would be delivered (n), calculated, per voxel, according to:

$$D_n = \frac{n}{2}\left(\sqrt{(\alpha/\beta)^2 + \frac{4}{n}EQD2(2+\alpha/\beta)}\right) - \frac{n}{2}(\alpha/\beta) \qquad \text{Eq. 1}$$

where α/β represents fraction size sensitivity.

STRIDeR re-irradiation planning

Data from 21 patients who previously received radical pelvic radiotherapy and who later received 5-fraction pelvic SABR for oligometastatic recurrence were used to illustrate the use of the pathway. Details of the planning process and stepwise approach to constraints and prescription dose are provided in Supplementary Material (S1 and Figure A1). Plans were compared to those produced using a standard manual method, described in Supplementary Material (S2 and S3).

EQD2 optimisation validation

For completeness, the EQD2 optimisation functionality was validated, as described in Supplementary Material (S6).

Results

STRIDeR re-irradiation planning

The STRIDeR pathway was used to produce re-irradiation plans in all cases (examples in Figure 3).

Based on the DIR assessment for bladder, DIR was considered reliable for dose mapping in all cases. For 13/20 cases where the rectum was within 5cm of the re-irradiation PTV, the rectal DIR was considered reliable for dose mapping.

Clinically acceptable plans were produced in 20/21 cases. 30Gy coverage and optimal constraints (Strategy 1a; Supplementary Material (Figure A1, Table A1)) were achieved in 12/21. In addition, 30Gy coverage was achieved with at least one OAR constraint being relaxed or by incorporating recovery, Strategies 1b and 1c, in 6 and 1 cases, respectively. Re-irradiation target location and previous dose influenced which constraint(s) had to be relaxed (Table A1). In one case, to achieve an acceptable plan, it was necessary to reduce prescription dose to 25Gy, relax constraints and accept under-coverage (Strategy 3). Here there was overlap between small bowel and the re-irradiation PTV, with limited OAR 'dose remaining' after original radiotherapy. In the final case, an acceptable plan was not achieved, again the result of limited OAR 'dose remaining'.

Outcomes from the manual planning process and comparisons with STRIDeR plans are presented in detail in Supplementary Material (S4, S5, Tables A1 and A2). In summary, compared to the manual method, the STRIDeR pathway resulted in similar coverage and OAR doses (based on equivalent prescription doses). In three cases (14%) STRIDeR plans required less OAR dose compromise (n=1) or permitted higher prescription doses (n=2; Supplementary Table A1).

Detail of the technical validation of the EQD2 objective functions can be found in Supplementary Material S7.

Discussion

Although re-irradiation is increasingly adopted, approaches to its use are variable, with no consistency in OAR dose constraints or strategies for dealing with anatomical change[4,6].

The incorporation of fraction size correction and tissue recovery as well as taking account of anatomical change are some of the main technical challenges when trying to meaningfully optimise re-irradiation treatments. To date, TPSs do not routinely incorporate radiobiology when evaluating cumulative doses and DIR may not be validated in the setting in which it would ideally be employed. The STRIDeR project aims to address these challenges in a clinical setting to facilitate a scientifically-driven and consistent methodology for optimising re-irradiation and evaluating cumulative OAR doses. Here we demonstrate a novel pathway within a commercial TPS and illustrate its use for radiobiologically meaningful re-irradiation optimisation. The STRIDeR pathway, using the original dose as background dose in selected OARs, was feasible and, in 14% of cases, resulted in plans requiring less constraint relaxation or permitted a higher prescription dose compared to plans generated using a more manual, planner-dependent method, where one constraint was conservatively applied to the entirety of the OAR.

Other groups have also acknowledged the difficulties in appropriately optimising re-irradiation plans. Pathways have been described that consider differences in fraction size, whereby original plans are reviewed to determine previous maximum OAR dose[14,15]. Based on cumulative constraints, 'doses remaining' for re-irradiation are determined; processes not dissimilar to our manual method. After planning based on these limits, physical dose and cumulative EQD2 plans are produced.

Previous work in this area, as summarised above, effectively generates re-irradiation plans separate to the previous dose distribution. In contrast, the novel methodology employed in STRIDeR optimises re-irradiation plans using the previous dose distribution as background dose. Resulting plans can be evaluated in EQD2 and in a specific number of fractions. Our implementation furthermore allows OAR-specific α/β values and tissue recovery; with values specified separately for each objective function, i.e. different values can be used for different objectives for the same OAR.

The STRIDeR pathway has the advantage that it sits within a commercially available TPS (albeit a research version currently). To our knowledge, we are the first to demonstrate EQD2 optimisation using a previous dose distribution as background dose within a commercial TPS. One study was identified that used a deformed, radiobiological background dose for re-irradiation optimisation in lung cancer[16]. This solution, however, existed external to the TPS and so could not be easily streamlined within routine practice. In addition, this solution was limited as only one planning objective could be applied per OAR whereas the STRIDeR solution allows multiple objectives. Furthermore, this approach set the background to 0Gy in the region of the re-irradiation PTV, which would limit optimisation of any portion of OAR within this volume, potentially generating a suboptimal plan. The STRIDeR pathway allows optimisation of OARs within the re-irradiation PTV.

The STRIDeR pathway allows flexibility as to which image registration approach is used: in the cohort evaluated, we opted not to disregard anatomical change and rely on solely RIR, nor did we fully 'trust' DIR. Instead, we adopted a selective approach to using DIR for dose mapping. Paradis et al based cumulative plans on RIR but are now evaluating DIR, which they acknowledge may be beneficial[14]. Price et al mainly used RIR, with some cautious use of DIR [15]. Richter et al describe a pathway for adaptive and re-irradiation planning[17]. Here,

RIR was used to view the original treatment on the re-irradiation planning CT to aid decision making. While these groups tend to employ RIR, and despite DIR not being the universal or recommended method for dose accumulation processes, DIR has been shown to be valuable for re-irradiation in several anatomical sites[7,18-22].

Optimal cumulative normal tissue constraints are largely unknown, with little robust data to guide these[23]. Some have been determined through consensus strategies, largely based on clinical experience[8,9]. The optimal constraints used for planning the cohort presented here were based on national guidelines[24] and were originally intended for de novo radiation. Therefore, when used in the cumulative manner described, these were unsurprisingly often too stringent to allow adequate target coverage. In these cases, a pragmatic stepwise approach was adopted, allowing increases in permitted doses, cautiously reflecting practice from elsewhere[25-27] or, for neural structures, increased incorporation of repair, cautiously extrapolating from spinal cord recovery work[28]. This allowed us to demonstrate some of the flexibility within the STRIDeR pathway. Where higher cumulative OAR doses are permitted than traditional de novo limits, this should be a conscious and justified decision, which considers anatomical and fractionation changes. The STRIDeR approach facilitates this and potentially reduces the risk of OAR overdose that may occur through misinterpretation of physically summated, RIR-based dose distributions[7].

There remains considerable uncertainty regarding the extent to which normal tissues recover after a first radiotherapy course and, indeed, which α/β values are most appropriate in the re-irradiation setting[23]. A standardised, cumulative, transparent, radiobiological approach, which considers previous and re-irradiation doses, as used here, alongside toxicity outcomes, may facilitate enhanced understanding of normal tissue recovery and re-irradiation α/β values.

There are further limitations to this process, beyond uncertainties in OAR re-irradiation constraints, recovery and α/β values. Firstly, DIR in the pelvis (and elsewhere) is imperfect. That said, deforming tissue into approximately the correct position, in the face of substantial anatomical change, provides more meaningful information for re-irradiation than relying solely on RIR. We adopted a pragmatic approach, only using DIR where it was considered most reliable and adopting a conservative approach elsewhere. Importantly, the STRIDeR pathway is not pelvis-specific so can be applied to any anatomical site but, before adoption, optimal image registration strategies must be evaluated. Secondly, the STRIDeR pathway is not yet available for clinical use within RayStation, but we are working towards this. Thirdly, many of our cases were from patients with nodal relapse of prostate cancer, where recurrences tended to occur on the previous field edge, rather than in the previous high dose (PTV) region (as was usually observed in rectal cancer cases). This represents the case mix we encounter in daily clinical practice. Further evaluation of the STRIDeR pathway in a greater number of patients, including with recurrences in previous higher dose regions and in a variety of sites, is warranted. Lastly, it could be questioned if the STRIDeR pathway provides advantages over the manual planning method, given that prescription and OAR doses were similar in most cases presented here. Our aim was not to demonstrate superiority of the STRIDeR pathway in terms of the resulting dose distributions: our aim was to describe the STRIDeR pathway and illustrate its use for re-irradiation treatment planning. That said, we found the STRIDeR pathway less laborious than the manual method, which requires multiple planner-initiated

stages and manual calculation of constraints. Any efficiency or time saving benefits, compared to more manual methods will, however, be formally assessed when the functionality is available in a clinical TPS release. In addition, while the manual method only allows one constraint to be conservatively applied across the entire OAR, the STRIDeR pathway allows voxel-by-voxel optimisation. Having described the pathway here, the benefits of voxel-by-voxel optimisation may be more apparent when evaluating it in other sites / higher dose region recurrences. Our further work will also evaluate pathway robustness, by assessing the impact of, for example, changes in α/β or mis-registration.

Conclusions

Re-irradiation is associated with several uncertainties. By incorporating anatomical change and radiobiology into plan optimisation, as in the STRIDeR pathway, more informed treatment decisions can be made. Developing scientifically-driven, transparent and standardised strategies to improve and learn from re-irradiation are essential to optimise the therapeutic ratio.

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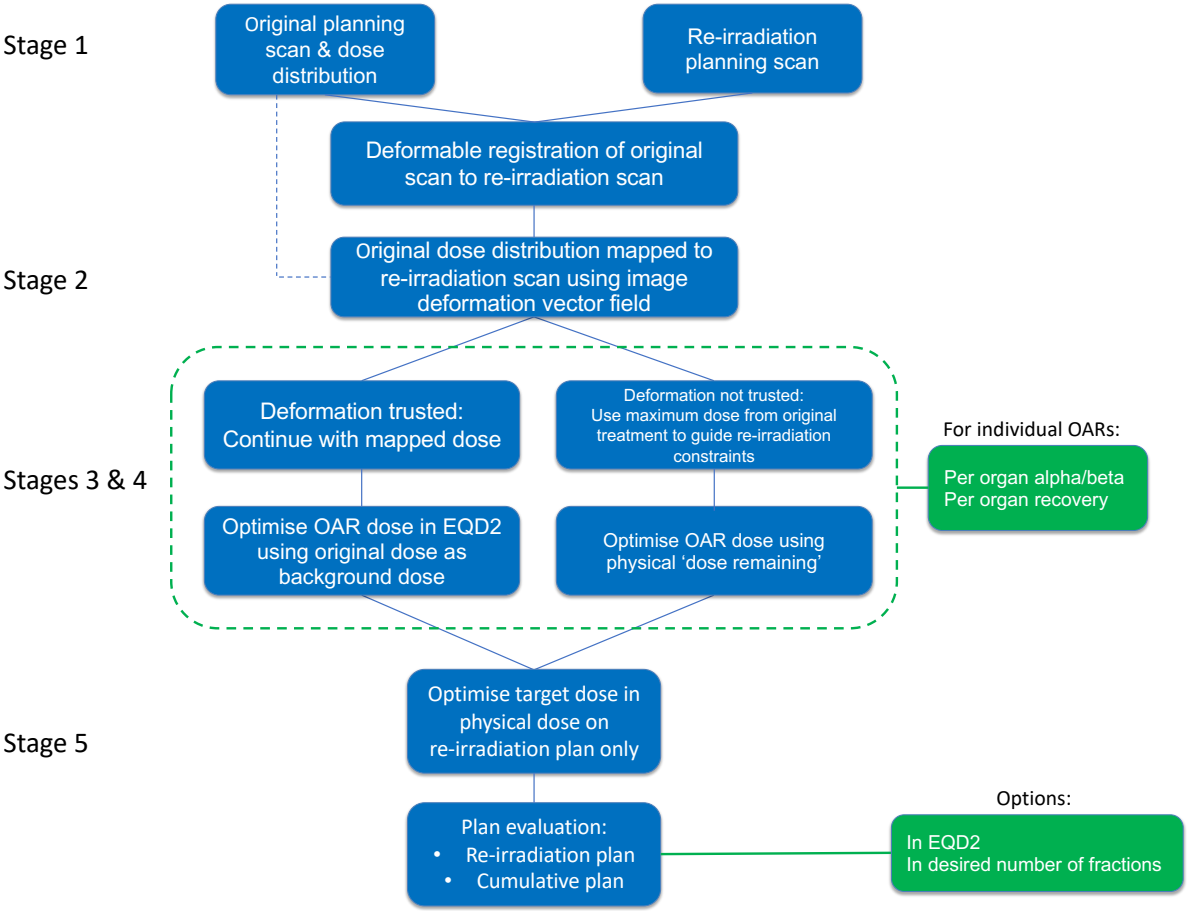
Figure legends

Figure 1. STRIDeR pathway for re-irradiation plan optimisation
EQD2: Equivalent dose in 2Gy fractions; OAR: organ at risk

Figure 2. Example optimisation console in RayStation. Cumulative organ at risk objectives are in EQD2 and are applied across both background and re-irradiation dose distributions for bladder, cauda equina, sacral plexus and vessels. Target objectives are in physical dose and applied to the re-irradiation dose distribution only. Objectives for colon and bowel also applied physically to the re-irradiation dose distribution only. α/β and recovery factors are specified per optimisation objective.
EQD2: Equivalent dose in 2 fractions; EUD: equivalent uniform dose; NT: normal tissue; PTV: planning target volume; reRT: re-irradiation

Figure 3. Examples of STRIDeR pathway and planning for oligometastatic bone (example 1) and nodal (example 2) recurrences. Re-irradiation GTV (red outline) and PTV (blue outline) copied onto original datasets (subfigures a and e) to illustrate position relative to previous treatment; original dose distributions deformed onto re-irradiation treatment scan and transformed to EQD2 (subfigures b and f); re-irradiation treatment plans in 5 fractions (subfigures c and g) and cumulative doses from original and re-irradiation treatments in EQD2 (subfigures d and h). Example 1: Original radiotherapy plan for prostate cancer, 76Gy in 37 fractions (subfigure a); note for the cumulative original and re-irradiation dose distribution in EQD2 (subfigure d) how the cumulative dose is shaped to avoid the posterior rectum with most dose anteriorly being due to the original treatment (cumulative D0.5cm^3 to rectum 75.3Gy EQD2 (α/β=3Gy)), and relatively low dose contribution to rectum from re-irradiation plan (subfigure 1c; D0.5cm^3 to rectum from re-irradiation plan 9.4Gy in 5 fractions, 9.2Gy in EQD2 (α/β=3Gy)). Example 2: Original radiotherapy plan for prostate bed radiotherapy, 52.5Gy in 20 fractions. Note (subfigure f) the 'pulling down' of isodoses to account for change in bladder shape and size; colon (peach outline above yellow bladder outline) therefore shown as being relatively spared from original radiotherapy due to fuller bladder at that time; three nodes in total are irradiated, all in different planes, hence other regions of lower dose visible.
EQD2: Equivalent dose in 2Gy fractions


Stage 1
Original planning scan & dose distribution
Re-irradiation planning scan
Deformable registration of original scan to re-irradiation scan
Stage 2
Original dose distribution mapped to re-irradiation scan using image deformation vector field
Stages 3 & 4
Deformation trusted: Continue with mapped dose
Deformation not trusted: Use maximum dose from original treatment to guide re-irradiation constraints
For individual OARs:
Per organ alpha/beta
Per organ recovery
Optimise OAR dose in EQD2 using original dose as background dose
Optimise OAR dose using physical 'dose remaining'
Stage 5
Optimise target dose in physical dose on re-irradiation plan only
Options:
Plan evaluation:
• Re-irradiation plan
• Cumulative plan
In EQD2
In desired number of fractions

Objectives/constraints | Beams | Control points | Protect | Treat | Beam dose specification points | Prescriptions | IDCAS collision avoidance

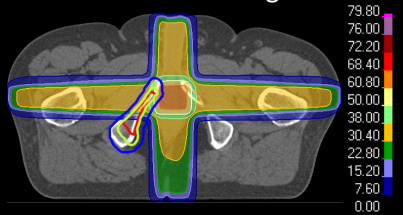
Add physical... | Add biological... | Edit... | Delete | Load template... | Save as template... | Add MCO function | Compute values

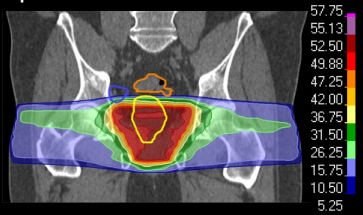
Function	Dose	ROI	Description	Weight	α/β [Gy]	Recovery
Physical composite objective						
Min dose	Beam set	PTV_reRT	Min dose 31.00 Gy	185.00		
Max dose	Beam set	PTV_reRT	Max dose 35.00 Gy	80.00		
Dose fall-off	Beam set	NT10	Dose fall-off [H]31.00 Gy [L]15.50 Gy, Low dose distance 1.00 cm	1.00		
Dose fall-off	Beam set	NT30	Dose fall-off [H]31.00 Gy [L]7.75 Gy, Low dose distance 3.00 cm	5.00		
Dose fall-off	Beam set	patient_both	Dose fall-off [H]31.00 Gy [L]5.00 Gy, Low dose distance 3.00 cm	5.00		
Max EUD	Beam set + background	bladder_reRT	Max EUD 72.50 Gy, Parameter A 150	20.00	3	0
Max EUD	Beam set + background	cauda_equina_reRT	Max EUD 60.50 Gy, Parameter A 150	20.00	2	0
Max dose	Beam set	colon_reRT	Max dose 30.00 Gy	20.00		
Max EUD	Beam set + background	left_fem_head_reRT	Max EUD 48.50 Gy, Parameter A 150	20.00	3	0
Max EUD	Beam set + background	rectum_reRT	Max EUD 60.20 Gy, Parameter A 150	20.00	3	0
Max EUD	Beam set + background	right_fem_head_reRT	Max EUD 48.60 Gy, Parameter A 150	20.00	3	0
Max EUD	Beam set + background	sacral_plexus_reRT	Max EUD 57.00 Gy, Parameter A 150	33.00	2	0
Max dose	Beam set	small_bowel_reRT	Max dose 23.40 Gy	50.00		
Max EUD	Beam set + background	vessels_reRT	Max EUD 130.00 Gy, Parameter A 150	20.00	3	0

Example 1: Previous prostate treatment, bone recurrence

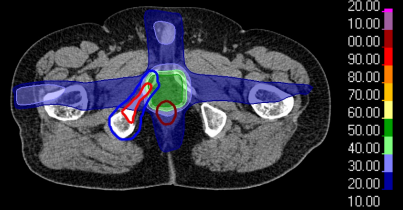
Example 2: Previous prostate bed treatment, nodal recurrence

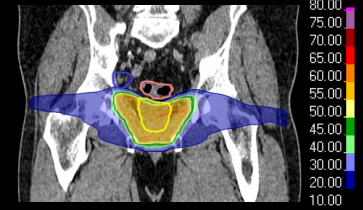
Original treatment plan



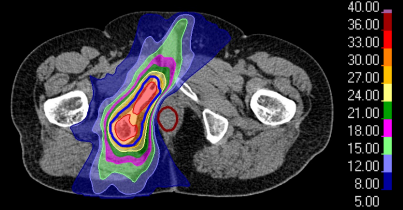


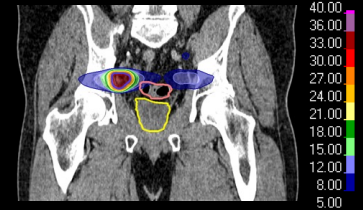
Original dose mapped onto re-irradiation scan



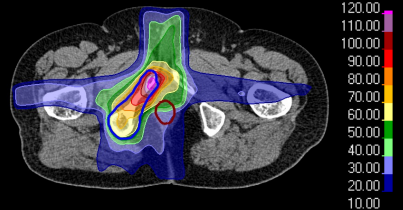


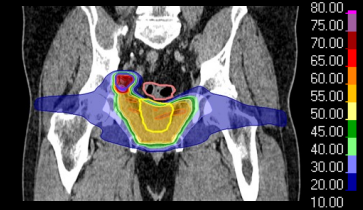
Re-Irradiation treatment plan





Cumulative doses in EQD2





Supplementary Material

S1. STRIDeR pathway planning

Data from 21 patients who previously received radical pelvic radiotherapy for prostate (n=17) or rectal (n=4) cancer and who later received 5-fraction pelvic SABR for oligometastatic recurrence were used to illustrate the use of the pathway. In 18 patients the re-irradiation targets were pelvic nodes (26 nodal lesions in total, no more than 3 per patient). For nodal targets, the gross tumour volume (GTV) was equal to the clinical target volume (CTV) and a 5mm isotropic margin was added to create the planning target volume (PTV). The remaining 3 patients had bony lesions (3 lesions in total, one per patient). Here the CTV was formed by adding a 3mmm isotropic margin to the GTV, which was then trimmed to bone. As for nodal targets, a 5mm isotropic margin was added to form the PTV. The patients whose data were used in the project had previously consented for SABR re-irradiation within a Research Ethics Committee (REC) approved NHS England Commissioning through Evaluation project (REC reference 16/NE/0285). Specific permission for use of the radiotherapy data within this project was provided from a REC-approved radiotherapy database management board (LeedsCAT, REC reference 19/YH/0300).

Re-irradiation plans were produced using the STRIDeR pathway aiming to deliver 30Gy in 5 fractions with 95% PTV coverage (D95%), while meeting optimal cumulative OAR constraints (Strategy 1a), based on existing clinical guidelines[1]. Where this could not be achieved, a stepwise process (Supplementary Figure A1) was adopted that allowed increasing constraint relaxation or incorporated increasing OAR recovery, in an effort to achieve coverage. Strategies 1a-1c used 30Gy prescription dose, with each strategy permitting increasing constraint relaxation / OAR recovery. If coverage could not be achieved at Strategy 1c, prescription dose was reduced to 25Gy and the same stepwise process followed, initially aiming to meet optimal constraints (Strategy 2a) but allowing increasing constraint relaxation / OAR recovery as necessary to achieve coverage (Strategies 2b and 2c). A final planning strategy, Strategy 3, maintained a prescription dose of 25Gy but PTV under-coverage was permitted in order to meet OAR constraints.

In circumstances where an OAR had received a dose close to or exceeding the cumulative constraint from the original radiotherapy alone, and where the additional contribution from the re-irradiation plan to the cumulative maximum ($D0.5cm^3$) dose was <1Gy EQD2, further constraint relaxation, prescription dose reduction or PTV under-coverage, according to the above stepwise process, were not attempted, given the minimal contribution from the re-irradiation plan. This situation was most often encountered where the inferior rectum had received a high dose (above cumulative constraint) at original radiotherapy, while the recurrence was positioned more superiorly, thus the contribution from the re-irradiation treatment to the previous high dose region was minimal.

For all normal tissues (including unspecified voxels) α/β=3Gy, except for cauda equina and sacral plexus where α/β=2Gy. Plans were generated using volumetric modulated arc therapy with sliding window sequencing. Planning was for an Elekta Versa LINAC (Elekta AB, Stockholm, Sweden) using a 360° arc, collimator and couch zero with 181

control points per arc. Calculations used a Collapsed Cone Convolution algorithm on a 0.25cm grid.

S2. Manual re-irradiation planning

STRIDeR plans were compared to those produced using a current manual method of re-irradiation planning, based on rigid image registration (RIR) with partial consideration of anatomical change (Figure A2). The manual pathway included the following stages:

1. *Assessment of maximum OAR doses from original radiotherapy*

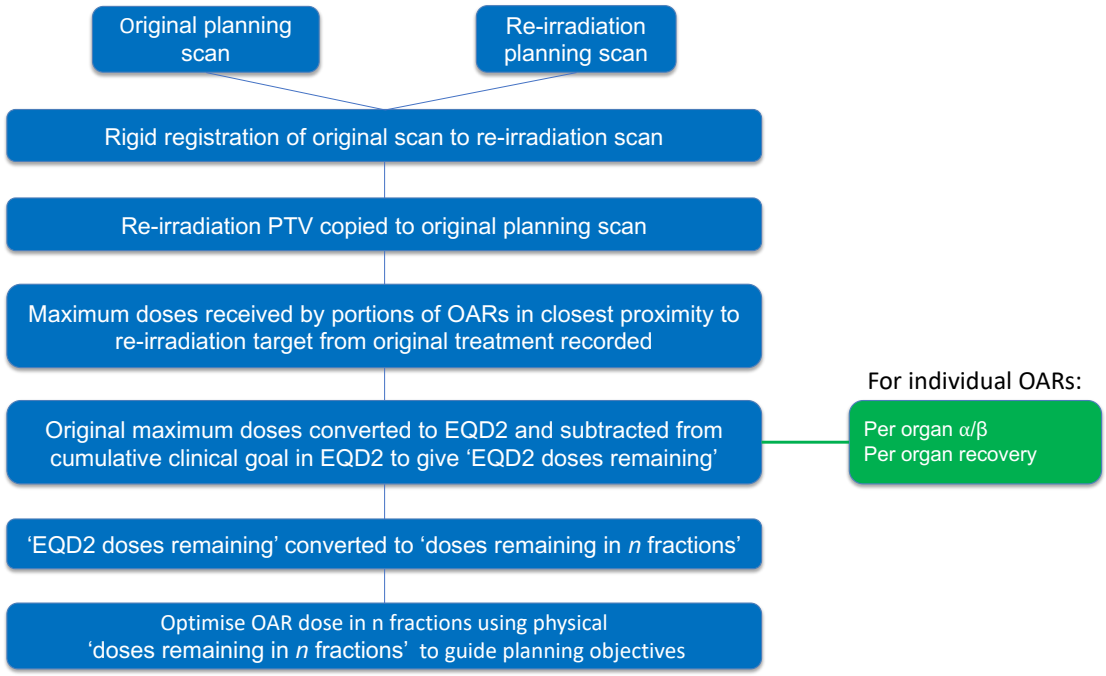
   The maximum dose received by the portion of an OAR in the original radiotherapy plan that was in closest proximity to the location of the re-irradiation target was considered the most relevant in the re-irradiation setting. To approximate this, the re-irradiation PTV was copied to the original radiotherapy dataset based on RIR using a bony match, prioritising the region around the re-irradiation target. To allow for potential positional change, for mobile/deformable structures, such as bowel and bladder, the maximum dose was that contained within a 2cm expansion of the re-irradiation PTV. For more fixed structures (nerves, vessels), the maximum dose was that contained within a 1cm expansion of the re-irradiation PTV (Supplementary Figure A3). Where the relevant OARs did not lie within a 2cm/1cm expansion of the re-irradiation PTV, concentric 1cm expansions were added until the OAR dose could be recorded. The maximum dose recorded was that to 0.5cm^3 of OAR, except for nerves, where 0.1cm^3 was used. This same process for determining maximum OAR doses was used within the STRIDeR pathway when the DIR was considered unreliable.

   The selection of 2cm / 1cm expansions around the re-irradiation PTV when determining previous maximum doses was pragmatic and guided by the typically rapid dose fall off associated with SABR. Of note, however, on final review of the combined plan, if a high cumulative normal tissue dose were to be noted beyond 2cm or 1cm of the re-irradiation target, and if this was considered to be because a considerably higher dose had previously been received by a relevant structure outside of the standard 2cm or 1cm expansion, compounded by additional dose as a result of the SABR treatment, then, if necessary, this stage of the optimisation process could be modified to consider the maximum dose to an OAR further from the re-irradiation target.

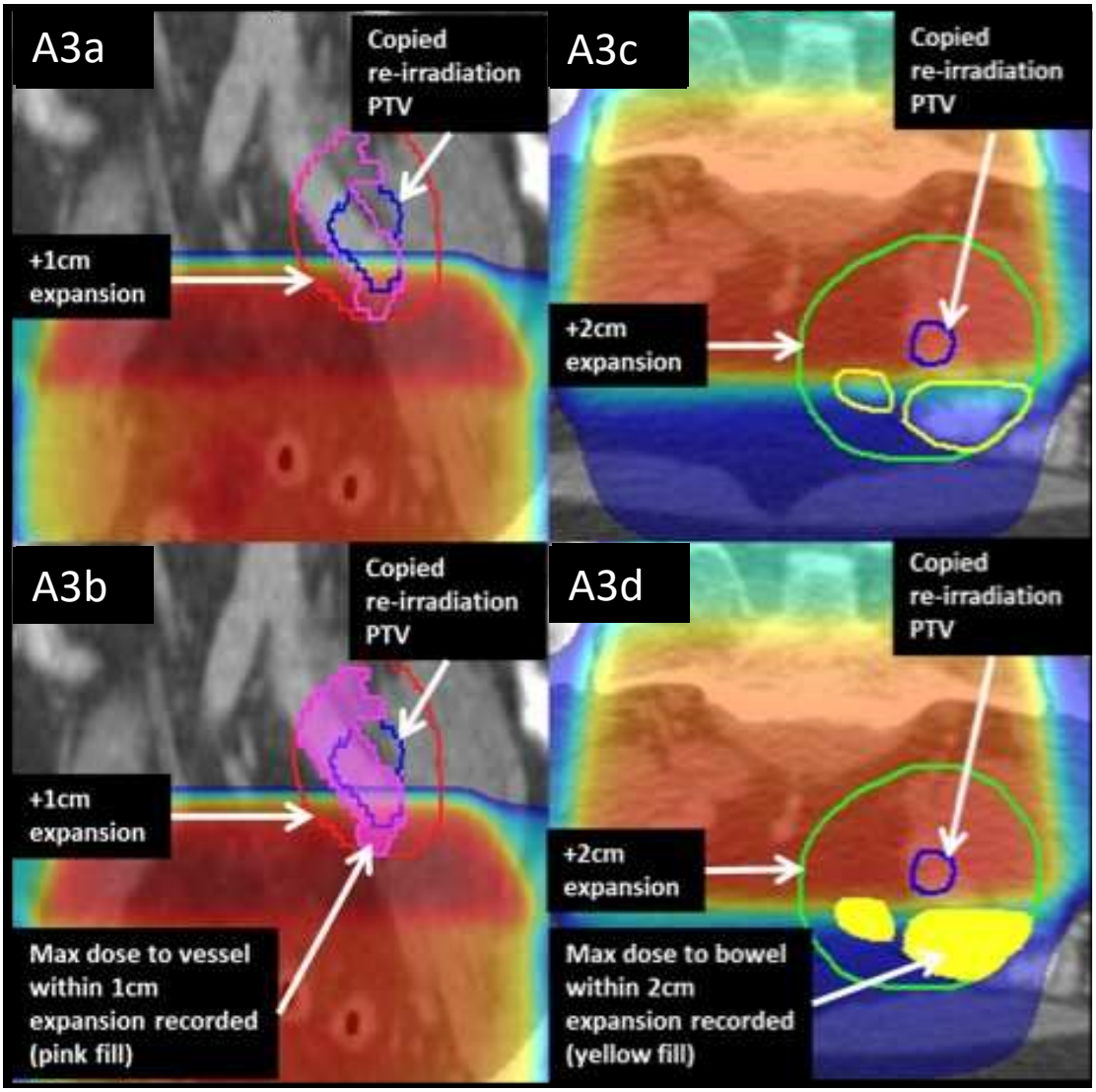
Supplementary Figure A1. Stepwise strategy for cumulative OAR constraints for STRIDeR pathway evaluation. Physical dose in five fractions shown with EQD2 in parentheses. α/β=3Gy for all normal tissues except for cauda equina and sacral plexus where α/β=2Gy. ALARA: as low as reasonably achievable; EQD2: Equivalent dose in 2Gy fractions. Optimal constraints based on[2]; partially relaxed and extended constraints based on cautious interpretation of/ extrapolation from [3-6].

	Strategy 1a (meet optimal constraints)		Strategy 1b (partially relaxed constraints)		Strategy 1c (allow extended bowel and plexus/cauda constraints)	Strategy 2a-c (prescription dose reduction)	Strategy 3 (prescription dose reduction and PTV under-coverage)
Bladder	D0.5cc <38Gy (80.6Gy)	If unable to achieve 95% coverage of PTV with 30Gy, then for OAR(s) causing coverage problem….. →	D0.5cc ALARA	If unable to achieve 95% coverage of PTV with 30Gy, then, for OAR(s) causing coverage problem….. →	D0.5cc ALARA	If unable to achieve 95% coverage of PTV with 30Gy and/or plan unacceptable, then drop prescription dose to 25Gy and follow same process → 25Gy	If unable to meet constraints and achieve 95% coverage with 25Gy, the accept under-coverage and follow same OAR process → 25Gy and under-cover as necessary
Cauda equina	D0.1cc <32Gy (67.2Gy) D5cc <30Gy (60Gy)		Allow 25% recovery on D0.1cc constraint Drop D5- ALARA		Allow 33% recovery on D0.1cc constraint Drop D5- ALARA		
Colon	D0.5cc <32Gy (60.2Gy)		D0.5cc <38Gy (80.6Gy)		D0.5cc<40.5Gy (89.9Gy)		
Left femoral head	D10cc <30Gy (54Gy)		ALARA		ALARA		
Rectum	D0.5cc <32Gy (60.2Gy)		D0.5cc <38Gy (80.6Gy)		D0.5cc<40.5Gy (89.9Gy)		
Right femoral head	D10cc <30Gy (54Gy)		ALARA		ALARA		
Sacral plexus	D0.1cc<32Gy (67.2Gy) D5cc<30Gy (60Gy)		Allow 25% recovery on D0.1cc constraint D5 ALARA		Allow 33% recovery on D0.1cc constraint Drop D5 ALARA		
Small bowel	D0.5cc<30Gy (54Gy) D5cc<25Gy (40Gy)		D0.5cc<35Gy (70Gy) D10cc<25Gy (40Gy)		D0.5cc<37.5Gy (78.8Gy) D15cc<25Gy (40Gy)		
Vessels	D0.5cc <53Gy (144.2Gy)		Unlikely to cause a coverage problem based on prescription dose		Unlikely to cause a coverage problem based on prescription dose		

Supplementary Figure A2. Manual method for re-irradiation plan optimisation. EQD2: Equivalent dose in 2 fractions; OAR: organ at risk; PTV: Planning Target Volume; *n* is number of fractions in which re-irradiation will be delivered.



Supplementary Figure A3. Manual approach to determine the original maximum dose in portion of an organ at risk in closest proximity to the re-irradiation target.
Subfigures A3a and A3b: For vessels and the sacral plexus, the re-irradiation PTV is copied onto the rigidly registered original radiotherapy plan and the maximum dose within a 1cm expansion recorded.
Subfigures A3c and A3d: To allow for more potential motion/ positional change, for bowel and bladder, the re-irradiation PTV is copied onto the rigidly registered original radiotherapy plan and the maximum dose within a 2cm expansion recorded.
If an organ at risk is not contained within a 1cm/ 2cm expansion then additional 1cm expansions are added until there is sufficient organ at risk contained to provide a dose.
PTV: Planning Target Dose



2. *Fractionation correction*

For each OAR the original dose was transformed to EQD2 according to:

$$EQD2_{\alpha/\beta\_original} = D\frac{{}^{D}/_{X}+\alpha/\beta}{2+\alpha/\beta} \qquad \text{eq. A1}$$

where X is the number of fractions in which the original radiotherapy was delivered, D is the total dose from the original treatment and α/β represents fraction size sensitivity.

3. *Incorporation of recovery (optional)*

Normal tissue recovery could be incorporated according to:

$$EQD2_{\alpha/\beta\_original(with\_recovery)} = (1-R) * EQD2_{\alpha/\beta\_original} \qquad \text{eq. A2}$$

where R is the proportion of recovery assumed in the interval between original radiotherapy and re-irradiation (a number between 0 and 1).

4. *Calculation of OAR 'dose remaining'*

The OAR 'Dose remaining' was determined by subtracting the original dose (+/- recovery) from a cumulative constraint (in EQD2):

$$EQD2_{\alpha/\beta\_dose\_remaining} = EQD2_{\alpha/\beta\_cumulative} - EQD2_{\alpha/\beta\_original(with\_recovery)} \quad \text{eq. A3}$$

5. *Transformation of OAR 'dose remaining' into number of fractions for re-irradiation*

The OAR constraints used for re-irradiation planning were the EQD2 'dose remaining' transformed into the number of fractions for re-irradiation according to:

$$D_n = \frac{n}{2}\left(\sqrt{(\alpha/\beta)^2 + \frac{4}{n}EQD2_{\alpha/\beta\_dose\_remaining}(2 + \alpha/\beta)} - \alpha/\beta\right) \qquad \text{eq. A4}$$

where n is the number of fractions in which the re-irradiation would be delivered and D_n is the dose that would provide the same effect if delivered in n fractions.
These constraints were used to determine the corresponding planning objectives, which were applied to the entire OAR.

6. *Re-irradiation planning*

   Plans were optimised using the same stepwise process as for those produced using the STRIDeR pathway (see above and Figure A1).

   For femoral heads, the maximum dose recorded was that received by $10cm^3$ and this was used to determine the 'dose remaining' $D10cm^3$ constraint for re-irradiation.

S3. Comparison between STRIDeR and manual plans

To allow more meaningful comparisons between the STRIDeR and manual plans, without the impact of the different image registration approaches, and to better reflect the cumulative doses that would have been delivered in practice, EQD2 cumulative doses (original + re-irradiation) were calculated for the manual plans using the same OAR registration approach for the STRIDeR pathway. In addition, where the STRIDeR pathway allowed a higher prescription dose than the manual method (i.e. 30Gy rather than 25Gy), STRIDeR cases were re-planned at 25Gy for the purpose of dose comparisons. The purpose of this comparison was not to attempt to demonstrate the STRIDeR pathway as superior but, instead, to illustrate the STRIDeR pathway in use and produce plans that were at least similar to those produced in clinical practice, where attempts to consider the impact of anatomical change and differences in fractionation schedules have also been incorporated.

Dose statistics for STRIDeR and manual plans were compared using the Wilcoxon Signed-rank exact test with $p<0.05$ considered statistically significant. Statistics were performed using SPSS version 27 (IBM Corp, Armonk, NY).

S4. Manual re-irradiation planning: results

Based on RIR and manual planning, clinically acceptable plans were produced in 20/21 cases, with optimal constraints achieved in 11/21. To achieve coverage, constraints were relaxed (Strategy 1b; n=6) and/or prescription dose was lowered (Strategy 2a; n=1, Strategy 2c, n=1; Supplementary Table A1). One case required reduced prescription dose, relaxed constraints, and under-coverage (Strategy 3; the same case as for STRIDeR planning), while in one case a clinically acceptable plan could not be produced (also the same case where this problem was encountered with STRIDeR planning). Evaluating cumulative doses (original + re-irradiation) in EQD2 based on the same image registration approach as used for the STRIDeR pathway resulted in no difference to the OAR objectives achieved and/or the achievable prescription dose (i.e., all plans remained categorised in the same strategy).

S5. Strider vs. manual pathway plan comparison: results

Compared to the manual planning method, the STRIDeR pathway resulted in three cases (14%) where plans required less OAR dose compromise (n=1, Strategies 1a vs. 1b for STRIDeR

vs. manual) or permitted higher prescription doses (n=2, Strategies 1b vs. 2a and 1c vs. 2c; Supplementary Table A1).

The two cases where coverage was achieved at 30Gy using the STRIDeR pathway but 25Gy using the manual pathway, were replanned at 25Gy using the STRIDeR pathway and these equivalent prescription dose plans were used for STRIDeR vs manual pathway comparison purposes. In this situation, median PTV $D_{95\%}$ for all cases with clinically acceptable plans (n=20), was 31.2Gy (range: 23.9-32.1) based on the STRIDeR pathway, which was not significantly different to that achieved with manual planning (median: 31.3Gy; range: 24.7-31.9). Median within patient difference was 0.1Gy (range: -1.1-1.6; STRIDeR minus manual).

There were no statistically significant differences between planning methods in cumulative doses to OARs where the DIR was accepted for dose mapping (Supplementary Table A2). For small bowel and colon (where previous maximum dose was used to guide constraints), there were also no significant OAR dose differences. Rectal doses were not significantly different when either DIR was accepted for dose mapping or when previous maximum dose was used to guide constraints. Median within patient differences between planning methods were small (Supplementary Table A2). Within patient differences of larger magnitude, where higher OAR doses were observed with the STRIDeR pathway, generally reflect the voxel-by-voxel optimisation within STRIDeR. Here, higher doses may be deposited in specific regions of OAR, depending on the previously received per-voxel dose. This contrasts with the manual method, where one constraint, based on previous maximum dose, is applied conservatively across the entire OAR. Where higher OAR doses were observed with the manual pathway, these were generally the result of achieving optimal rather than mandatory constraints using the STRIDeR pathway. Smaller differences may relate to these factors and/or differences in optimisation choices.

Supplementary Table A1. Planning strategies achieved based on different planning methods

Case	STRIDeR pathway		Manual method	
	Planning Strategy	OARs requiring relaxation of constraints/ recovery incorporation where applicable	Planning Strategy	OARs requiring relaxation of constraints/ recovery incorporation where applicable
1	3	Small bowel	3	Small bowel
2	1a		1a	
3	1b	Rectum	1b	Rectum
4				
5	1b	Small bowel	1b	Small bowel
6	1b†	Sacral plexus; 30Gy prescription dose	2a	25Gy prescription dose required to meet constraints
7	1b	Bladder	1b	Bladder
8	1a		1a	
9	1a		1a	
10	1b	Sacral plexus	1b	Sacral plexus
11	1a		1a	
12	1b	Small bowel	1b	Small bowel
13	1c†	Small bowel; 30Gy prescription dose	2c	Small bowel; 25Gy prescription dose required to meet constraints
14	1a		1a	
15	1a†		1b	Rectum
16	1a		1a	
17	1a		1a	
18	1a		1a	
19	1a		1a	
20	1a		1a	
21	1a		1a	

†Plans requiring less constraint relaxation/ recovery or where a higher prescription dose feasible compared to manual method

In case 4, a clinically acceptable plan could not be achieved.

Supplementary Table A2. Organs At Risk (OAR) dose metrics

	Threshold volume (where relevant)	STRIDeR planning pathway		Manual plans		Within-patient difference (STRIDeR minus Manual)	
OARs where DIR accepted for dose summation (cumulative dose in EQD2; Gy)							
		Median of Maximum doses to 0.5cm^3† (range)	Median Dose to threshold volume (range)	Median of Maximum doses to 0.5cm^3† (range)	Median Dose to threshold volume (range)	Median of Maximum doses to 0.5cm^3† (range)	Median Dose to threshold volume (range)
Rectum	-	60.8 (42.1-81.4)	-	60.8 (42.1-81.4)	-	0.0 (-2.3 - 0.0)	-
Vessels	-	65.6 (33.9-90.5)	-	65.4 (35.6-87.1)	-	0.1 (-1.7 – 5.7)	-
Sacral plexus†	5cm^3	50.6 (23.6-66.9)	25.7 (6.8-59.7)	51.1 (23.6-71.7)	24.1 (6.5 - 59.1)	0.0 (-6.0 - 6.2)	0.1 (-0.8 - 1.7)
Cauda equina†	5cm^3	11.7 (0.7-61.9)	9.4 (1.3-36.2)	10.3 (0.7-65.3)	9.1 (1.3 - 34.5)	0.0 (-3.3 - 1.3)	0.3 (0.0 – 1.7)
Bladder	15cm^3	61.2 (41.3-110.5)	59.5 (34.6-79.9)	61.1 (41.3-111.1)	59.5 (34.6 - 79.9)	0.0 (-0.6 - 8.3)	0.0 (-0.1 - 7.0)
Left femoral head	10cm^3	40.1 (18.5-58.6)	33.4 (17.1-47.5)	39.2 (18.5-58.6)	33.4 (17.1- 47.7)	0.0 (-0.3 - 0.0)	0.0 (-0.4 - 3.0)
Right femoral head	10cm^3	40.5 (8.4-64.2)	35.4 (5.5-50.9)	40.5 (8.4-63.3)	35.4 (5.5- 50.5)	0.0 (-1.8 - 0.4)	0.0 (-0.9 - 1.0)
OARs where DIR rejected for dose summation and therefore previous maximum OAR dose to guide re-irradiation constraint (re-irradiation dose in 5 fractions; Gy)							
Small bowel	5cm^3	13.8 (0.3-31.2)	10.6 (0.2-22.1)	13.8 (0.3-30.8)	10.6 (0.2-19.7)	0.1 (-1.2 - 2.6)	0.0 (-2.1 - 6.5)
Colon	-	13.0 (7.0-30.6)*	-	12.2 (6.2-29.8)	-	0.1 (-0.5 – 1.5)	-
Rectum	-	5.5 (0.4-13.9)	-	5.7 (0.4-12.1)	-	-0.1 (-0.5 – 1.8)	-

†D0.1cm^3 used for maximum sacral plexus and cauda equina dosimetry,

DIR: Deformable image registration; EQD2: Equivalent dose in 2Gy fractions; STRIDeR: Support Tool for Re-Irradiation Decision guided by Radiobiology

S6: EQD2 optimisation validation

Five patient cases were used to validate the EQD2 optimisation functionality by testing whether or not the re-irradiation plan OAR dose statistics were similar based on a fixed cumulative OAR objective and fixed background *EQD2* but with alteration in:

1. Number of fractions (5, 10, 20 and 30 fractions, based on α/β = 3Gy, i.e. for a background dose EQD2 of 60Gy, the background prescription dose was: 31.95Gy in 5 fractions, 41.78Gy in 10 fractions, 53.05Gy in 20 fractions and 60Gy in 30 fractions);
2. Proportion of recovery (0%, 25%, 50% and 75%, based on α/β = 3Gy, i.e. for a background dose EQD2 of 60Gy, the background prescription dose was: 31.95Gy in 5 fractions (0% repair), 37.84Gy in 5 fractions (25% repair), 47.79Gy in 5 fractions (50% repair) and 70.32Gy in 5 fractions (75% repair)).

Thus, in each patient a uniform physical background dose, covering the entire patient volume, was simulated that kept the EQD2 of the background dose constant. Re-irradiation plans were then optimised for a single OAR in closest proximity to, but not overlapping with, the re-irradiation PTV. In the case of changes in the number of fractions, the cumulative EQD2 objective used for optimisation was constant. In the case of changes in the proportion of recovery, the cumulative objective used for optimisation allowed the same proportion of recovery as that assigned to the background dose. In all cases, if the EQD2 cost function is functioning correctly, the resulting OAR dosimetry (see below) should be very similar. Supplementary Figure A4a outlines this test set up.

Validation of the EQD2 optimisation in regard to the α/β value required a different approach, as changes in α/β impact the EQD2 objective in both the background and re-irradiation dose distributions. For each value of α/β assessed (1, 3, 6 and 9Gy), doses were calculated in EQD2 for a constant physical dose delivered in both the original plan and reirradiation plan i.e. for a background dose of 30Gy in 5 fractions the background EQD2 would be 70.0Gy (α/β = 1), 54.0Gy (α/β = 3), 45.0Gy (α/β = 6) and 40.9Gy (α/β = 9); for a replan dose of 20 Gy in 5 fractions the replan EQD2 would be 33.3Gy (α/β = 1), 28Gy (α/β = 3), 25.0Gy (α/β = 6) and 23.6Gy (α/β = 9). These EQD2 doses were then summated to give the cumulative EQD2 objective used for optimisation i.e. 103.3Gy (α/β = 1), 82.0Gy (α/β = 3), 70.0Gy (α/β = 6) and 64.6Gy (α/β = 9), which should all be equivalent during optimisation if α/β handling by EQD2 cost function is correct. Supplementary Figure A4b outlines this test set up.

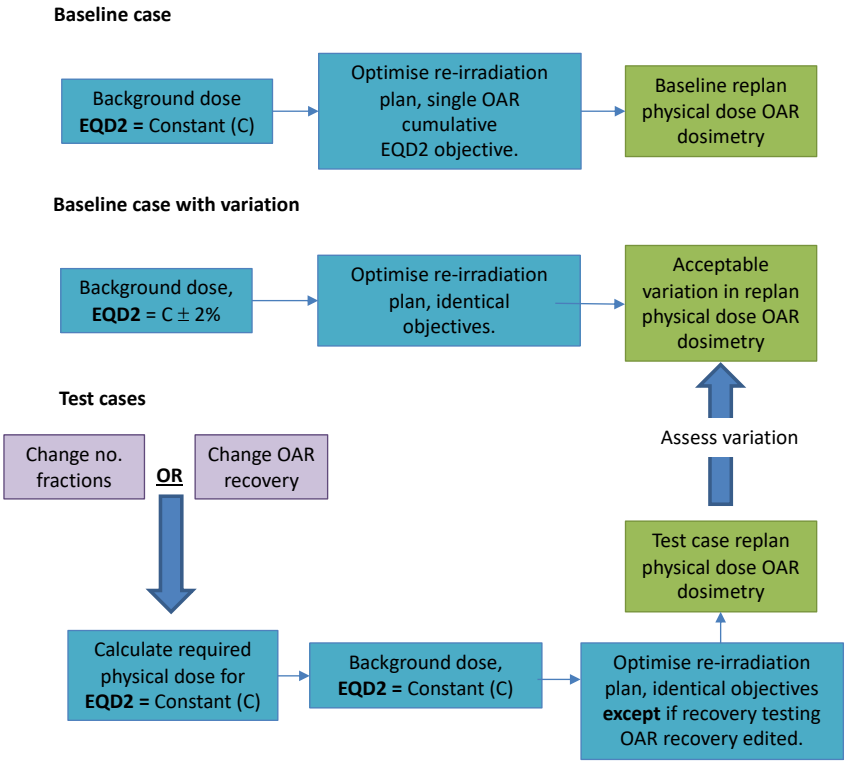
In all tests, a pass of the assessment of similarity was OAR D0.1, 0.5, 1.2, 3.0, 5.0 and 10.0 cc within values obtained by for a baseline plan optimised with +/-2% introduced EQD2 error.

Initial investigations showed background dose selection had a significant impact on test sensitivity, which was due to the behaviour OAR objective functions also considering background dose. The general behaviour found is shown in Supplementary Figure A5. It can be seen that the objective has most impact on planning in approximately the middle range of background dose and has least impact at very low (when there is little need to apply the objective) and very high (when the objective cannot have an impact as the previous dose is so high) background doses. Validation tests therefore used a baseline background EQD2 for a single OAR mid-way between doses D1 and D2 for maximum test sensitivity, where the

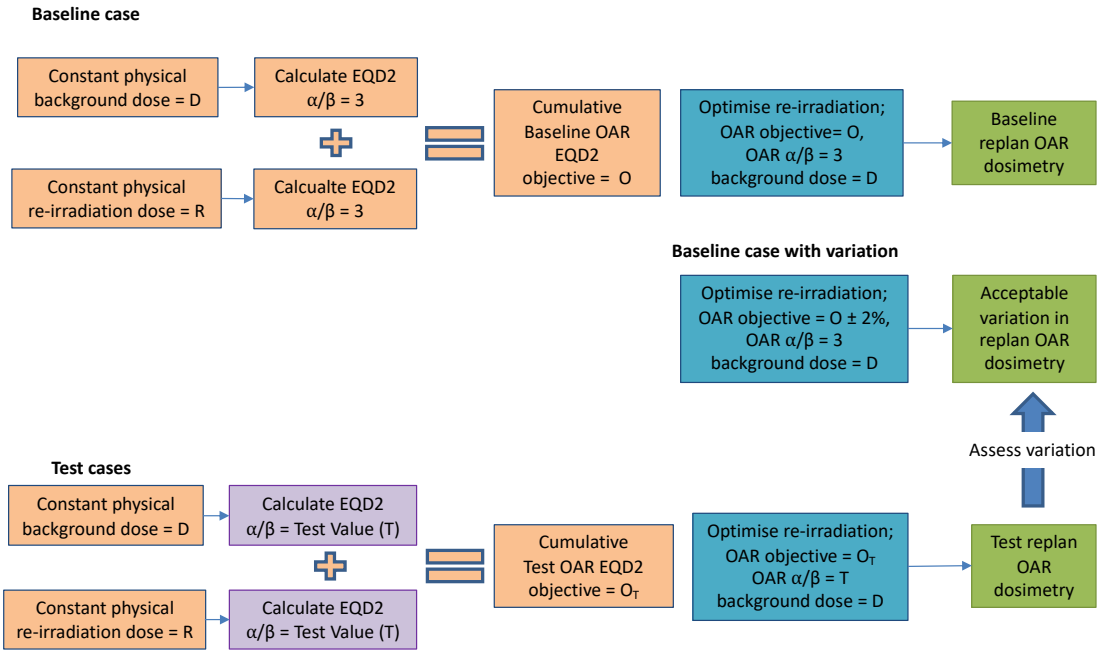
lower (D1) and upper (D2) are the background doses between which the OAR objective function had capacity to impact on re-irradiation dose.

Supplementary Figure A4. Strategies to validate EQD2 optimisation.
Subfigure A4a: Strategy to validate EQD2 optimisation by varying number of fractions or proportion of recovery.
Subfigure A4b: Strategy to validate EQD2 optimisation by varying α/β value.
EQD2: Equivalent dose in 2Gy fractions; OAR: Organ at risk

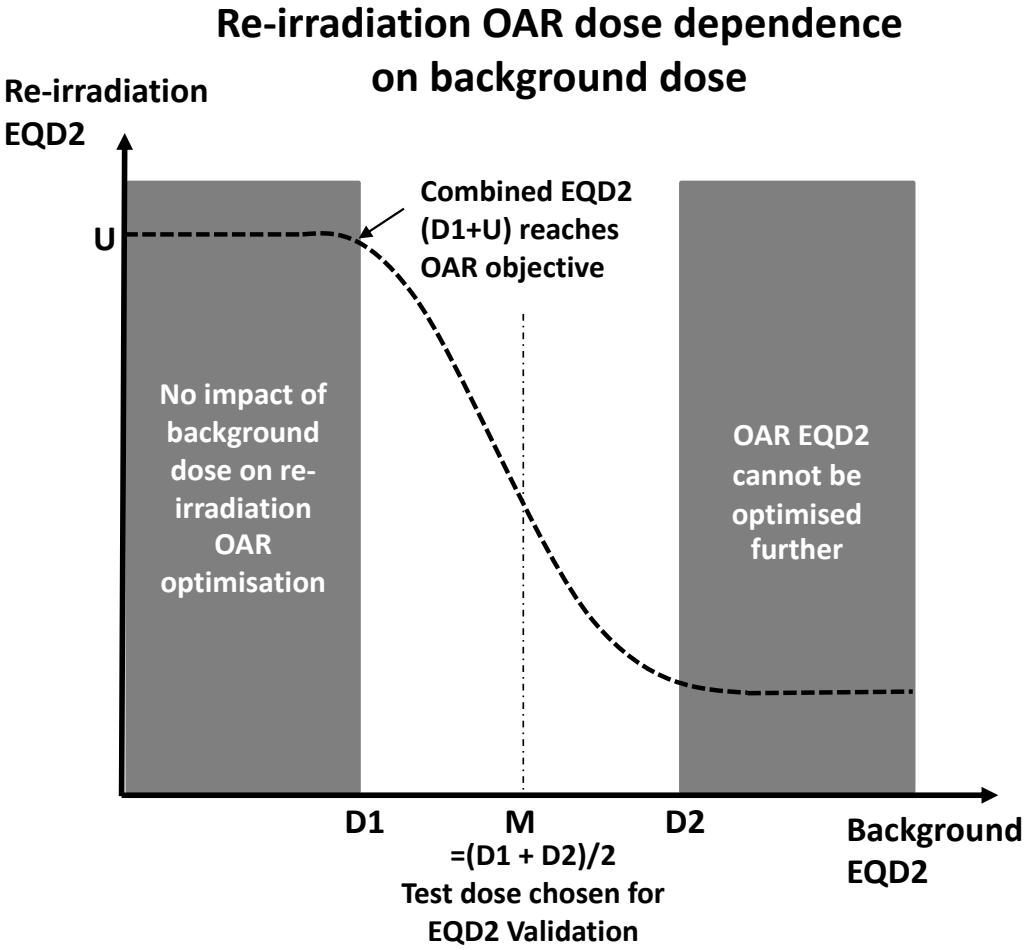
A4a



A4b.



Supplementary Figure A5. General case relationship between applied uniform background EQD2 and resultant re-irradiation EQD2 for a plan with a single fixed OAR objective. U is the upper limit on the re-irradiation dose alone in the absence of any background dose. For an organ with objective C the objective begins to reduce OAR dose at dose D1, when U plus D1 is approximately equal to C. The objective can continue to reduce OAR dose until dose D2, at which point the target objective begins to exceed the OAR objective. Therefore, the objective function only has capacity to reduce organ doses to a lower limit of organ sparing between D1 and D2. As such, the dose selected for the testing was at a mid-point M, between D1 and D2 for maximum test sensitivity. M was determined per patient by plotting the patient specific curve using sample plans. EQD2: equivalent dose in 2Gy fractions; OAR: organ at risk



S7. EQD2 optimisation validation: results

For all five patient cases used in the validation work, when evaluating different degrees of recovery and changes in fractionation, variation in OAR/PTV dosimetry was within the +/-2% control case and so passed the assessment of similarity. Similarly, for changes in α/β, in all scenarios, OAR/PTV dosimetry was within +/- 2% of the control.

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