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Original Article

Multi-centre evaluation of variation in cumulative dose assessment in reirradiation scenarios

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ABSTRACT

Background and Purpose: Safe reirradiation relies on assessment of cumulative doses to organs at risk (OARs) across multiple treatments. Different clinical pathways can result in inconsistent estimates. Here, we quantified the consistency of cumulative dose to OARs across multi-centre clinical pathways.

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Dose accumulation
Image registration

Material and Methods: We provided DICOM planning CT, structures and doses for two reirradiation cases: head & neck (HN) and lung. Participants followed their standard pathway to assess the cumulative physical and EQD2 doses (with provided α/β values), and submitted DVH metrics and a description of their pathways. Participants could also submit physical dose distributions from Course 1 mapped onto the CT of Course 2 using their best available tools. To assess isolated impact of image registrations, a single observer accumulated each submitted spatially mapped physical dose for every participating centre.
Results: Cumulative dose assessment was performed by 24 participants. Pathways included rigid (n = 15), or deformable (n = 5) image registration-based 3D dose summation, visual inspection of isodose line contours (n = 1), or summation of dose metrics extracted from each course (n = 3). Largest variations were observed in near-maximum cumulative doses (25.4 – 41.8 Gy for HN, 2.4 – 33.8 Gy for lung OARs), with lower variations in volume/dose metrics to large organs. A standardised process involving spatial mapping of the first course dose to the second course CT followed by summation improved consistency for most near-maximum dose metrics in both cases.
Conclusion: Large variations highlight the uncertainty in reporting cumulative doses in reirradiation scenarios, with implications for outcome analysis and understanding of published doses. Using a standardised workflow potentially including spatially mapped doses improves consistency in determination of accumulated dose in reirradiation scenarios.

Introduction

Reirradiation with curative intent is increasing in frequency due to improvements in patient outcomes and availability of modern precision radiotherapy techniques, such as image guidance and dose sculpting capabilities [1]. Safe reirradiation requires reliable assessment of cumulative doses to critical organs, contending with anatomical changes between treatment courses and radiobiological effects from fraction size and tissue recovery [2]. Retrospective evaluations of reirradiation clinical outcomes that include assessment of cumulative doses have been reported for a range of tumour sites [3–10]. These form a basis for estimation of what doses can be delivered safely in a reirradiation scenario, and importantly where caution must be exercised due to high risk of significant side effects.

Registration of original treatment planning imaging to the reirradiation scans can aid mapping of previously treated dose distributions (or isodose lines) to the current anatomy. This may involve rigid or deformable image registration (RIR, DIR), and may be performed using a global image registration applied to the whole image, or to specific organs or regions of interest [2,6,11–17]. Paradis et al. detailed a standardized reirradiation process including registrations and tables of consensus-based biologically effective dose constraints and tissue recovery factors [13]. The recently published ESTRO-EORTC consensus statement on reirradiation echoed those findings, noting that some level of dose mapping must be attempted, as well as conversion to bioeffective doses [1,18].

The process of dose mapping and radiobiological dose rescaling is not straightforward, however [11,19]. Variation in cumulative dose assessment between institutions may arise from differences in image registration approaches based on available software or expertise, computation of bioeffective doses, and use of tissue recovery factors. Such variation in assessment pathways may introduce variation into the cumulative dose assessment thereby limiting the potential to relate the clinical toxicity to the actual delivered dose and hindering outcome modelling. Even though accumulation of doses from the current and previous courses is recognised as a cornerstone to understand the clinical toxicity limits in reirradiation [13,18], the impact of this variation has not previously been explored. We performed a multi-centre evaluation of cumulative reirradiation dose assessment. The aim was to identify institutional processes for assessment of reirradiation cumulative doses, to quantify variation in cumulative dose to critical organs among participating institutes, and to evaluate variation due to spatial registration-based mapping of doses in reirradiation scenarios.

Materials & methods

All participants of the ESTRO 2022 Physics workshop 'Reirradiation: Improving dose summation for plan optimisation, evaluation, and outcomes analysis' were invited to participate. We surveyed participants to elicit data on participants' clinical reirradiation assessment workflow (Supplementary Material 1). The survey questionnaire was constructed and shared via Google Forms.

To quantify the variation in cumulative dose assessment between observers, two typical clinical reirradiation cases were provided: a head and neck (HN) cancer and a lung cancer case, Fig. 1. These two cases were selected as they provided different fractionations necessitating conversion to EQD2, contained a range of critical organs with varying levels of deformation, and included both near maximum and mean/volumetric dose metrics. *The HN case* was from a patient with cancer of unknown primary in the head and neck region who received 70 Gy in 35 fractions in *Course 1* followed by 59.4 Gy in 33 fractions in *Course 2*, two years later. The patient was simulated arms down, with a thermoplastic mask for immobilisation in both courses and in *Course 2* the patient was simulated with a bite block. The need for ethics review for *the HN case* was waived by the Peter MacCallum Cancer Centre privacy officer due to de-identified nature of the data shared. *The lung case* was from a patient with non-small cell lung cancer who received 55 Gy in 8 fractions in *Course 1* followed by 45 Gy in 30 fractions in *Course 2,* 1.5 years later. The patient was simulated with arms up for both courses. Approval for use of *the lung case* of data for use in research was provided under the LeedsCAT radiotherapy research database umbrella (reference 19-YH-0300); with further permission for anonymised data sharing for the purpose of this project provided by the Leeds Teaching Hospitals NHS Trust Caldicott Guardian. The cases, in the form of anonymised DICOM data sets, were shared with the participants; with each data set consisting of the planning CT images, the structure sets and radiation dose files from *Course 1* and *Course 2*. A summary of the two methods used for interobserver variation in cumulative dose assessment is provided in Fig. 2.

Method 1: Cumulative doses assessed using institutional methods.

Participants were asked to follow their institutional protocols and methods for reirradiation dose assessment for each case, with software systems commissioned for clinical practice at the participant's institution. Quantitative measures of accumulated dose for the two cases were collected in the second part of the questionnaire. The collected dose metrics included the cumulative near maximum ($D_{1\%}$ or $D_{0.1cc}$), and volumetric physical and EQD2 doses to specific critical organs deemed to be of clinical relevance. Only EQD2 was requested in this survey, regardless of the bioeffective dose conversions used in the institutes' standard clinical pathways. The dose metrics were selected to represent reirradiation clinical protocols in use at the investigators' centres. To minimise one source of variation, participants were provided with α/β ratios for all organs and instructed to use these (rather than values specified in local protocols). An α/β of 1 Gy was used for the spinal cord,

2 Gy used for the brachial plexus, 2.5 Gy for the pericardium and 3 Gy for all other organs. The variability in determining the region of specific critical organs receiving the highest cumulative dose was estimated by collection of the spatial location of the maximum cumulative dose for critical organs from each participant.

Method 2: Cumulative physical doses assessed using spatially mapped dose distributions.

In an attempt to quantify the inter-observer variation in cumulative doses only from the registration process, each observer performed one registration per case (as opposed to registration for each organ, as used by some observers). The participants were asked to provide the *Course 1* physical dose spatially mapped to the image set of *Course 2* for each case. The process could involve RIR or DIR and did not need to follow the participant's clinical practice. The mapped physical 3D dose distributions were submitted to one investigator who imported all participants' dose distributions into a treatment planning system (Eclipse, v16.1, Varian Medical Systems, Palo Alto, USA). Each participant's dose grid was added to the *Course 2* dose on the *Course 2* image, and the cumulative physical dose metrics listed in the previous section were extracted using the Eclipse Scripting Application Program Interface. This process effectively removes all variation other than that introduced by the image registration and dose resampling. The F-test was used to compare the variance between the cumulative physical doses obtained by participants using their clinical workflows, and 3D dose mapping processed by a single observer. Only those observers who submitted to both components of the study were included when computing the F-test, and cumulative doses that included tissue recovery factors were excluded from this comparison.

Results

We received survey data from 25 participants consisting of medical physicists, radiation therapists / dosimetrists, and one representative from industry. Survey data were received from Europe (n = 20), and one each from the USA, Canada, Australia, Turkey and Saudi Arabia. The median participant-reported estimated number of institutional reirradiation cases per year was 100 [range 30 – 2000]. The industry representative was excluded from analysis of clinical pathways. The survey responses for clinical pathways in reirradiation assessment can be found in the Supplementary Material 2.

The majority of centres (20/24) used the record and verify system (R&V) or electronic medical record software (EMR) to indicate a reirradiation prescription; ten of these utilised specific physics/RTT task notification in the patient's pathway. Informal methods such as email or phone calls or physical paper forms to notify the treatment planning team of a reirradiation scenario were utilised as the primary method (3/24) or in combination with EMR or R&V notification (5/24) by a minority of participants. Three participants also indicated that this documentation included description of specific critical organs with concerns of increased toxicity, and specific EQD2 parameters to be used. All centres imported previous DICOM planning images, structures, plans, and dose distributions when available. Some centres also utilised plan reports or screenshots, or re-created treatment plans using previous treatment data when DICOM data was not available. The majority of participants reported using EQD2 scaling in their clinical workflow (17/24), and/or BED (8/24). Tissue recovery factors were routinely used by 14/24 respondents, ranging from 25 % to 75 % depending on the organ and time since last irradiation.

Institutional methods for performing assessment of cumulative dose to critical organs according to Method 1 included RIR (n = 15) or DIR (n = 5)-based summation of 3D doses, visual inspection of isodose line contours copied from *Course 1* to *Course 2* image sets after RIR (n = 1), or summation of dose metrics extracted from each course without registration (n = 3). One participant submitted two sets of cumulative doses, based on either point dose summation or RIR based dose mapping, as both processes were utilised in clinical practice. RIR was performed either globally based on the spinal cord (n = 2), *Course 2* GTV (n = 1), per specific organ of interest (n = 5), or unspecified (7). Despite 14 participants indicating that they in general use tissue recovery factors, only three participants used tissue recovery factors of 25–50 % in the HN case; one participant applied them to the spinal cord only and two applied them to all organs.

Fig. 3 shows the variation in cumulative dose metrics among participants and institutional methods for the two cases, with the median and ranges summarised in Table 1. For the HN case, the inter-observer range in near maximum ($D_{1\%}$ or $D_{0.1cc}$) among all organs of interest

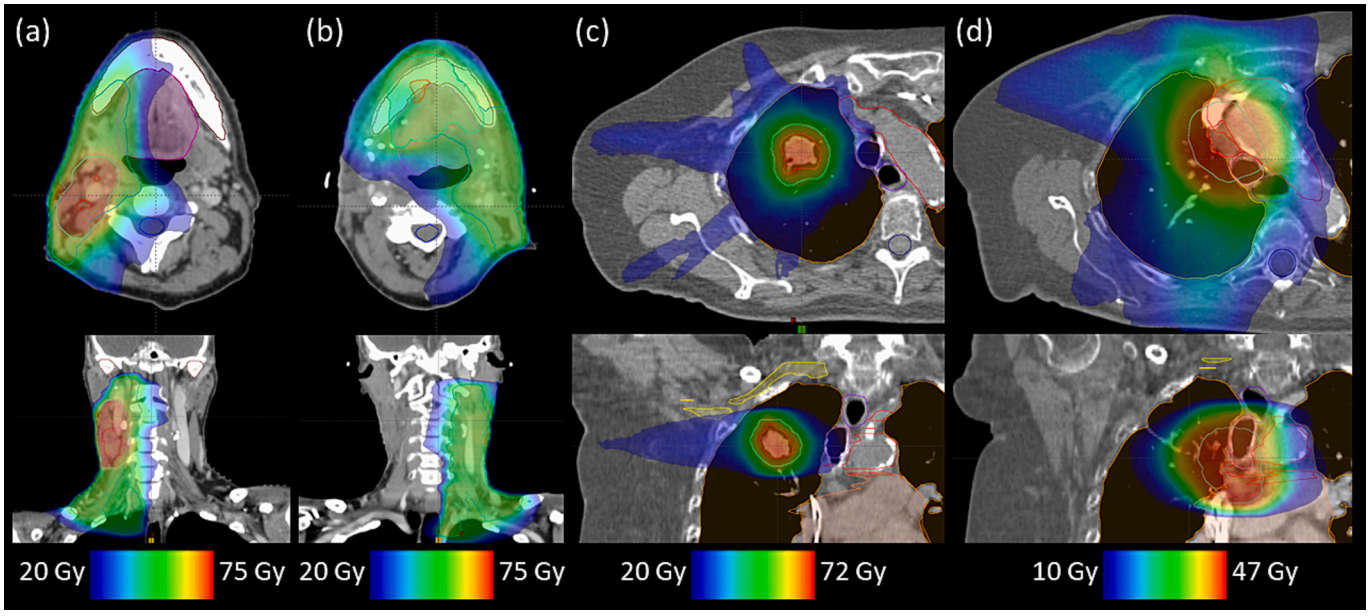

Fig. 1. Axial (top row) and coronal slices (bottom row) and dose distributions for (a) Course 1 and (b) Course 2 for the head & neck (HN) cancer case. The GTV (red), CTV (cyan), PTV (blue), oral cavity (pink) and mandible (brown) are shown. (c) Course 1 and (d) Course 2 for the lung cancer case. The GTV (red), PTV (cyan), spinal cord (dark blue), trachea (pink), vessels (red), oesophagus (purple), brachial plexus (yellow), lungs (orange) and pericardium (dark orange) are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was up to 41.8 Gy, and the inter-observer range in mean oral cavity dose was 20.2 Gy. The largest variation arose from inclusion of tissue recovery factors; excluding these, the inter-observer range was reduced to 24.1 Gy or less (near maximum doses) and 9.0 Gy (mean oral cavity dose), and the interquartile ranges among all critical organs were between 2.6 Gy and 5.5 Gy. For the lung case, the inter-observer range in near maximum ($D_{1\%}$ or $D_{0.1cc}$) among all organs of interest was up to 33.8 Gy, in mean lung dose was 0.6 Gy, and in lung V_{20Gy} was 1.2 %. For the HN case, the largest inter-observer range in near maximum doses decreased to 23.4 Gy after conversion to EQD2. For the lung case however, the largest inter-observer range in near maximum doses increased to 42.9 Gy after conversion to EQD2.

The difference in the position of maximum dose from the average position reported for all observers for each OAR is shown in Fig. 4; and the median, inter-quartile range and range provided in Supplementary Table 1. For the HN case, the range in maximum dose locations in each OAR was up to 3.7 cm, however the inter-quartile range was within 1.5 cm. The 3D vector distance from each location of maximum dose from the mean position of all observers was up to 2.9 cm (mandible). For the lung case, the range in maximum dose locations in each OAR was within 4.5 cm, however the inter-quartile range was within 0.5 cm. The 3D vector distance from each location of maximum dose from the mean position of all observers was up to 3.1 cm (brachial plexus).

For the HN case, 14 (58 %) spatially mapped dose distributions for assessment via Method 2 were submitted using DIR (n = 12) and RIR (n = 2) and for the lung case, 12 (50 %) mapped dose distributions were submitted using DIR (n = 9) and RIR (n = 3). DIR algorithms included Deformable multipass (n = 5, VelocityAI), VoxAlign (n = 3, MIM), ANACONDA (n = 2, RayStation), and Demons (n = 2, Pinnacle, Prosoma). Fig. 5 shows the cumulative physical dose metrics for all structures in both cases when using *Course 1* doses mapped to the *Course 2* image based on RIR or DIR. Table 1 provides the median and range of these dose metrics. Up to 18.8 Gy variation in near maximum dose and 5.6 Gy for the oral cavity mean dose were observed for the HN case. Up to 13.5 Gy variation in cumulative near maximum doses, and only 0.6 Gy and 0.7 % for the mean lung and lung V20 Gy, respectively, were observed in the lung case.

The variance in the cumulative dose metrics obtained via institutional clinical methods (excluding those where tissue recovery factors were used) compared with those obtained via observers performing a single image registration with RIR and DIR, or DIR alone, is in Supplementary Table 2. For the HN case, using spatially mapped doses via a single image registration per observer reduced the variance for the mandible $D_{1\%}$, oral cavity $D_{1\%}$ (both $p < 0.05$), but not for the oral cavity mean dose ($p = 0.18$) or spinal cord $D_{0.01cc}$ ($p = 0.80$). If the cumulative doses obtained only via DIR dose mapping were considered, these results were the same. Similarly for the lung case, using mapped doses via a global image registration decreased the variance for all metrics ($p < 0.01$) with the exception of lungs mean ($p = 0.56$) and lungs V_{20Gy} ($p = 0.73$). If only DIR dose mapping was considered, the variance was reduced with a global registration approach for all metrics ($p < 0.05$) except for lungs mean dose ($p = 0.47$) and lungs V_{20Gy} ($p = 0.68$).

Discussion

Reirradiation is increasing in frequency, but a critical component of safe and effective reirradiation is accurate and robust evaluation of cumulative critical organ doses. Inaccurate cumulative dose assessment can result in excess risk of side effects (if underestimated) or underdosing of target volumes (if overestimated), and skew understanding of cumulative dose impacts on outcomes in clinical trials or cohort studies. We have demonstrated substantial variation in clinical practice when performing reirradiation assessments; in particular with respect to image registration approaches, use of tissue recovery factors, and use and methods of obtaining cumulative EQD2. The large variation observed highlights the uncertainty in reporting cumulative doses in reirradiation scenarios, indicating a need for improved consistency in methodology and reporting. As expected, there was less variation in

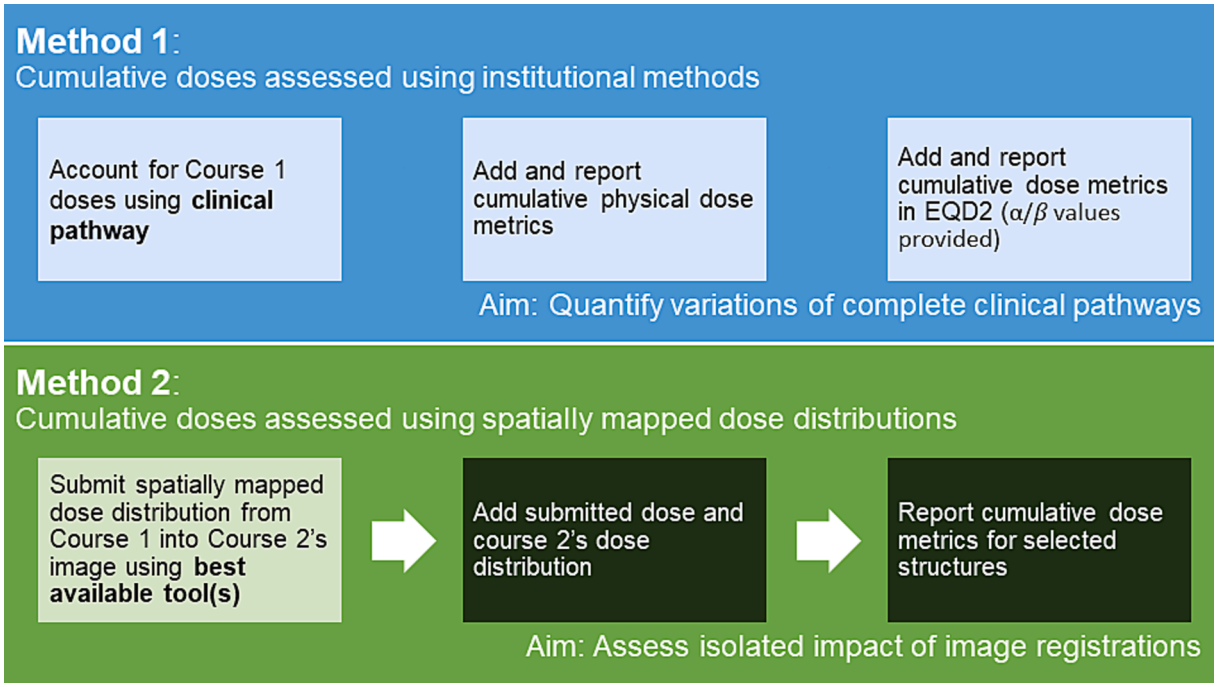

Fig. 2. Graphical presentation of the two methods used to quantify cumulative doses in our analysis. For Method 1, each participant was tasked to follow their institutional pathway (including applying tissue recovery factors) to estimate cumulative dose metrics and report these in physical dose and EQD2 (with provided α/β values). For Method 2, each participant used their best available tool to spatially map the dose of the Course 2 onto the image of Course 2, and submit this mapped dose to a single researcher. The researcher added the spatially mapped dose from Course 1 to the Course 2 dose and extracted the cumulative physical doses. Blocks with light filling represent steps executed by participants in their institutions, while the dark blocks indicate the steps performed by the researcher leading the analysis.

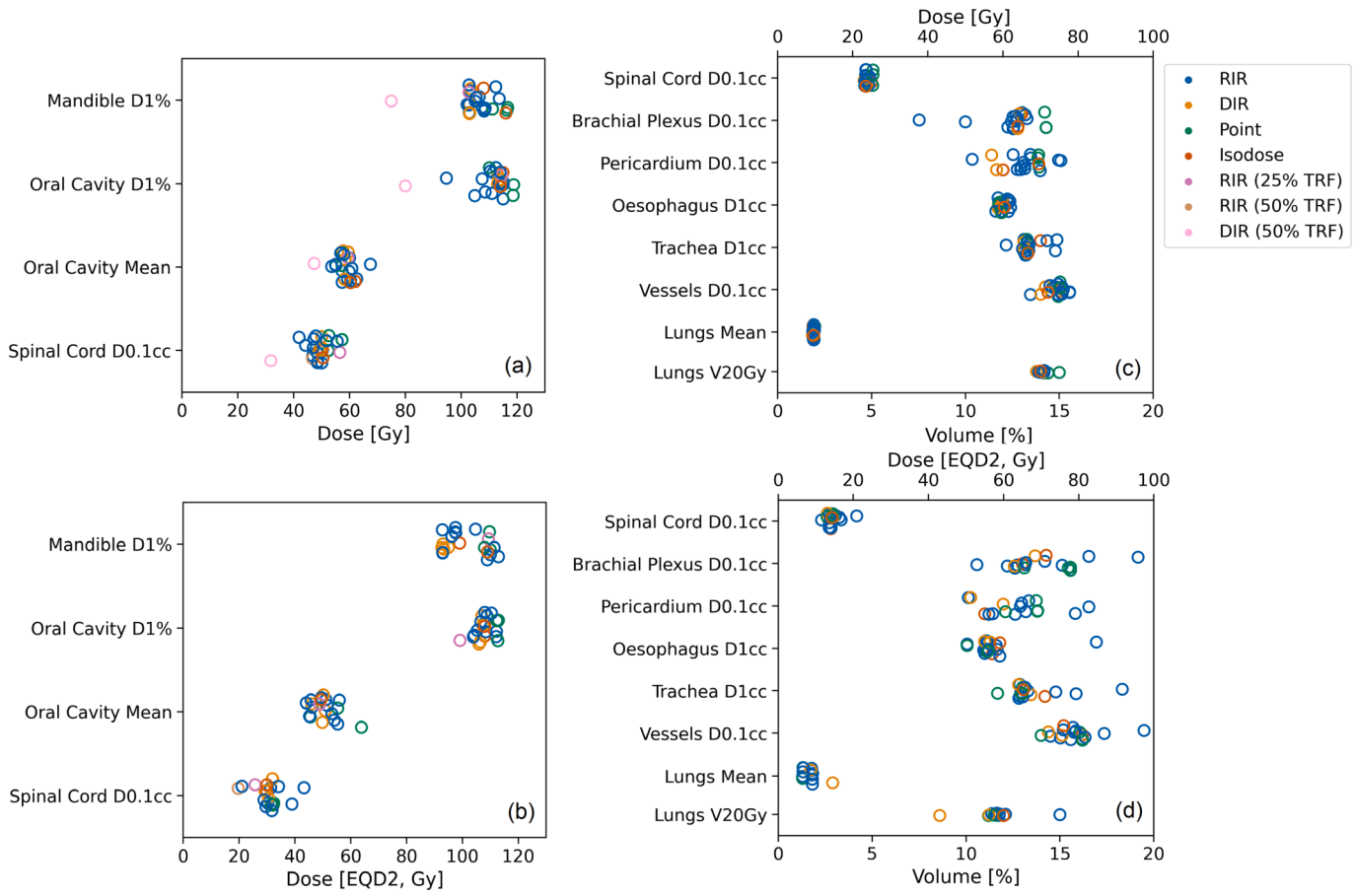

Fig. 3. Cumulative physical (a & c) and EQD2 (b & d) dose metrics including those where tissue recovery factors (TRF) were used for the HN cancer case (a & b) and lung case (c & d); as extracted from the survey based on Method 1 (institutional clinical practice for reirradiation dose assessment).

volume dose metrics to large organs such as the lung.

Assessment of cumulative doses in reirradiation can be both challenging and time consuming. Consequently, use of a single image registration to map doses is an attractive proposition. When observers used a single image registration (typically DIR) the variation in cumulative dose to a number of critical organs reduced compared with institutional clinical approaches. There was, however, residual variation in cumulative dose metrics when DIR was used in the first component of the study. This may indicate that it was not only the use of DIR but also a consistent process of mapping 3D dose and summation which may reduce the variation. Use of a single image registration is appealing from an efficiency point-of-view; multiple RIR based on each critical organ is resource intensive, whereas DIR minimises the need for organ-specific rigid registration. Use of DIR for this purpose, however, requires a high level of vigilance with respect to accuracy of the registration and the complexities of deforming absorbed dose distributions [20].

DIR may not always be feasible, and it should be noted that we were not able to determine accuracy of spatially mapped doses with RIR or DIR, only consistency between observers, software, and algorithms. Further, in many instances DIR may have substantial limitations in dealing with large changes in anatomy between each treatment course, such as appearing/disappearing tissue and structures [20]. Indeed, in the HN case evaluated in this study, there was a bite block in one image but not in the other. In this particular patient, however, the bite block was at a distance from the high dose overlap, potentially limiting its impact on the registration accuracy and accumulated dose in the oral cavity. Although these are potential major limitations to using DIR routinely, the uncertainties introduced by using DIR may be less than if deformable spatial mapping of doses was not used [21]. It must be noted that RIR has potential for substantial errors in dose mapping, particularly in organs with large deformations. However, given the potential catastrophic impacts of mis-estimation cumulative doses to critical organs in reirradiation, an estimate of the uncertainty of cumulative doses should be performed, regardless of the approach [20–23]. A limitation of the current study is that our results are only likely applicable for scenarios such as those investigated, where there were relatively limited changes in patient position or anatomy. There may be instances where there are larger anatomical variations (such as bladder filling), significant weight changes, arm position, head extension, prone or supine positioning which may result in larger variation between algorithms and processes used. It is critical to evaluate accuracy of spatially mapped doses, with any available method such as visual inspection.

The location of maximum dose was used as a surrogate for the high dose region for specific organs important in plan optimisation in reirradiation. This location is subject to high uncertainty, however, given that there are often multiple nearby points receiving a similar high dose. The variation in location of maximum dose for structures such as the spinal cord and brachial plexus was largest along the length of the nerve (SI direction for the spinal cord, LR direction for the brachial plexus). High isodose lines in treatment plans often span a distance along these nerves; registration based on the vertebra may result in multiple locations along the length of the spinal cord receiving near the maximum cumulative dose. Further, larger variation was observed for the mandible for the HN case. The region of the mandible containing the locations of maximum dose is where the high dose from both plans overlaps. As such, the dose in the *Course 2* plan was optimised to drop off quite rapidly in this part of the mandible. We thus had quite high dose gradients in this area, which increased sensitivity to variations in

Table 1
Median and range of cumulative dose metrics as extracted from the survey based on institutional clinical practice of reirradiation dose assessment, or using a single image registration per observer based on RIR or DIR.

Metric	Method 1. Institutional clinical methods		Method 2. Spatial mapping method
	Dose [Gy] Median (IQR) Range	*Dose [EQD2, Gy]* Median (IQR) Range	*Dose [Gy]*Median (IQR) Range
Mandible D1%	105.2 (5.5) 74.9 – 116.7	97.6 (16.0) 92.6 – 112.9	102.6 (0.8) 98.5 – 109.2
Oral Cavity D1%	113.4 (4.4) 80.0 – 118.8	108.0 (4.5) 99.1 – 112.9	113.2 (1.5) 103.4 – 114.4
Oral Cavity Mean	58.2 (2.6) 47.3 – 67.5	50.2 (7.6) 44.0 – 63.8	58.9 (1.7) 54.3 – 59.9
Spinal Cord D0.1 cc	48.9 (3.7) 31.9 – 57.3	31.0 (2.7) 19.8 – 43.2	48.7 (2.0) 37.7 – 56.5
Spinal Cord D0.1 cc	23.6 (0.9) 23.0 – 25.4	14.3 (1.0) 11.6 – 20.9	23.6 (0.2) 23.3 – 23.9
Brachial Plexus D0.1 cc	63.9 (2.6) 37.7 – 71.5	68.4 (13.2) 52.9 – 95.8	64.0 (0.7) 62.5 – 65.3
Pericardium D0.1 cc	65.8 (6.0) 51.8 – 75.4	64.5 (11.6) 50.6 – 82.7	57.7 (4.1) 53.4 – 67.0
Oesophagus D1cc	59.6 (2.5) 58.1 – 62.0	55.8 (2.5) 50.3 – 84.7	58.8 (0.1) 58.5 – 59.1
Trachea D1cc	66.4 (1.3) 60.9 – 74.4	65.1 (2.7) 58.4 – 91.6	65.6 (0.3) 64.8 – 67.0
Vessels D0.1 cc	74.7 (2.9) 67.3 – 77.8	78.7 (5.3) 70.0 – 97.4	71.3 (2.8) 70.0 – 75.0
Lungs Mean	9.6 (0.1) 9.3 – 9.9	8.9 (2.5) 6.5 – 14.5	9.4 (0.2) 9.0 – 9.6
Lungs V20 Gy	14.1 (0.1) 13.8 – 15.0	11.6 (0.5) 8.6 – 15.0	13.9 (0.3) 13.5 – 14.2

registration.

Conversion to EQD2 resulted in increased range in cumulative doses for some organs. It was assumed that accumulated EQD2 was obtained via summation of EQD2 from each course. The variation in methodology of computing cumulative doses thus likely propagated into EQD2 summation, resulting in the observed variation in cumulative EQD2. Such variation in conversion methodology highlights the lack of available tools and software to support radiobiological dose conversion in clinical workflows [24]. In this study, consistent α/β values were provided; there may be variation in these values used by different institutions. When using few fractions, such as in stereotactic reirradiation, small variations in α/β can substantially change calculated bioeffective doses. It is a potential limitation of the current study that we did not specify for the participants whether to use (or not) tissue recovery factors; resulting in further variation in reported cumulative doses.

Research aiming to establish relationships between treatment side effects and cumulative delivered dose to critical organs in reirradiation scenarios is reliant on reported (cumulative) dose to organs at risk. However, the observed variations in clinical practice highlight the need for standardised approaches. When analysing and reporting on any reirradiation dose data, the method used for dose accumulation, cumulative dose without accounting for recovery, and dose metrics in physical dose (in addition to biologically equivalent dose) should be provided [13]. For prospective registries or clinical trials, it may be prudent to prescribe a methodology for determining cumulative doses; this should be performed in consultation with recruiting institutions to determine a minimum achievable workflow based on available technology and expertise. For example, RIR-based spatial mapping of doses, on a per-organ basis (for relevant critical organs) is likely achievable regardless of the treatment planning system. Note that it may be challenging to enforce a specific method for clinical decisions, given clinical and patient-specific factors such as response to radiation, and available resources and software. Alternatively, a third party such as a trial quality assurance central review team may perform the accumulation using a consistent and reproducible methodology.

As recently highlighted, efficient image registration (likely deformable) to drive spatial mapping and summing of dose distributions, coupled with voxel-wise conversion of dose to bioeffective doses, are ranked as high priorities in reirradiation assessment [24]. Consistency in these components is critical for treatment plan optimisation in the reirradiation context [23,25]. To achieve this, a critical aspect is quantifying the uncertainty and variation in spatial mapping of doses between images. For DIR, assessment of uncertainty from what appear to be physically 'plausible' registrations is critical, as is ensuring the registration is adequate at the region of overlap of dose from multiple

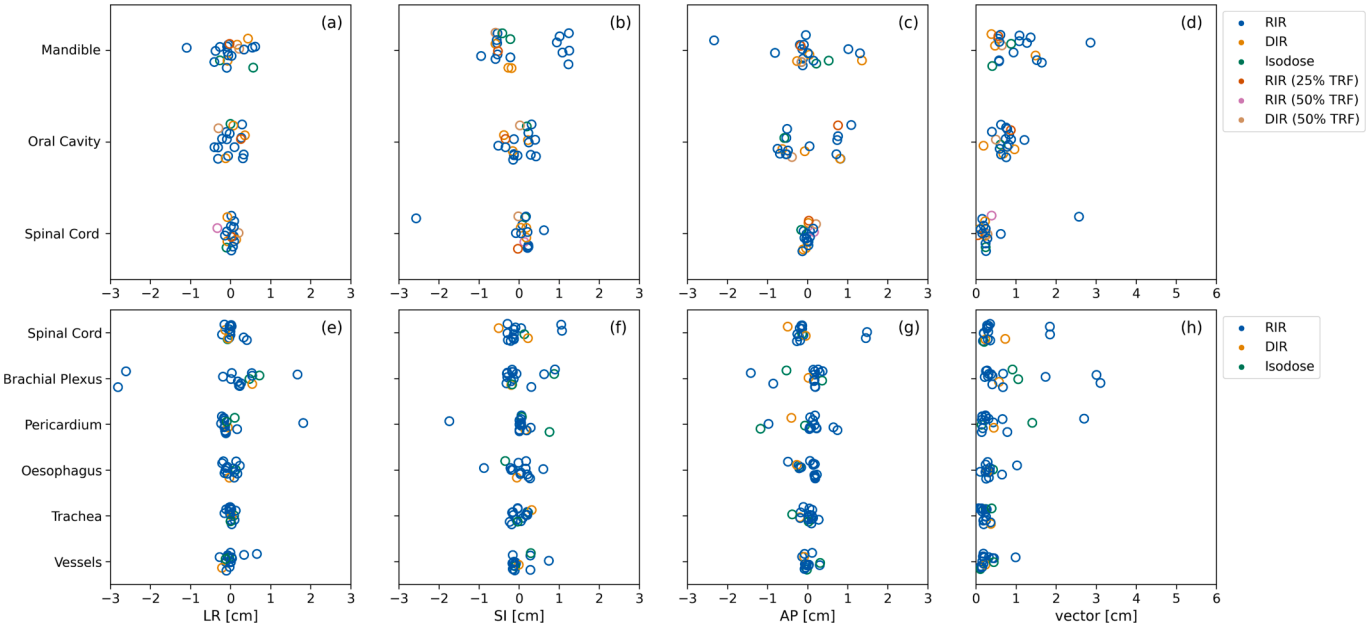

Fig. 4. (a) and (e) left–right (LR), (b) and (f) superior-inferior (SI), (c) and (g) anterior-posterior and (d) and (h) 3D vector variation in the position of maximum dose in each direction from the average position of all participants for each critical organ in the HN cancer and lung cases respectively. This was extracted from the survey based on Method 1 (institutional clinical practice for reirradiation dose assessment).

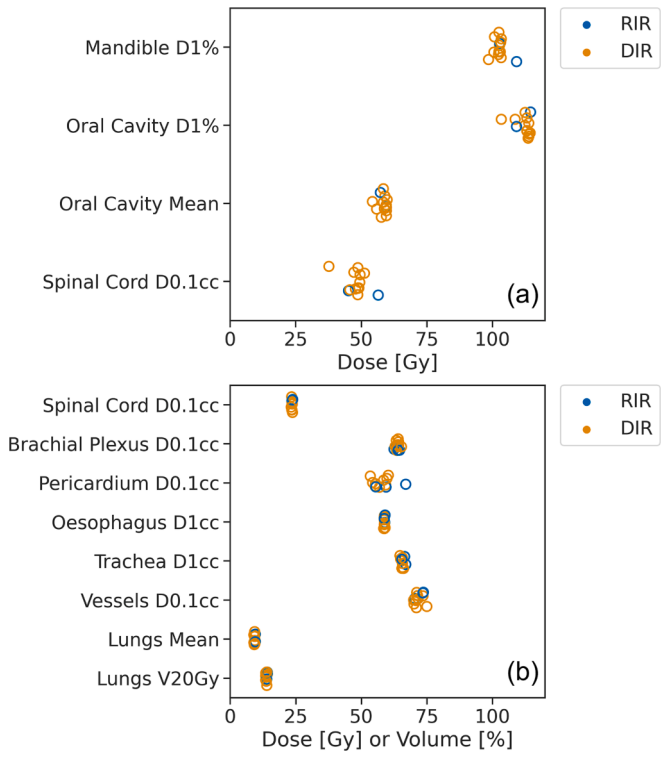

Fig. 5. Cumulative dose metrics achieved for (a) HN cancer case and (b) lung cancer case as extracted from Method 2 (single observer summation of Course 2 dose with Course 1 dose distributions as mapped to the Course 2 image set by local image registration processes).

courses. It may be hypothesised that implementation of these processes in routine clinical software with use of standardised radiobiological parameters may improve consistency in reported doses in reirradiation scenarios.

Conclusions

Differences in methods for spatial mapping of dose between courses, conversion to bioeffective doses, and use of tissue recovery factors resulted in substantial interobserver variations in cumulative near maximum dose assessment in two reirradiation scenarios. There was less variation in volumetric dose metrics such as mean dose and lung V_{20Gy}. Deformable image registration may present a more consistent approach when compared to other pathways. However, there still remains some variation between observers, and validating accuracy and quantifying uncertainty of spatially mapped dose distributions are critical.

CRediT authorship contribution statement

Nicholas Hardcastle: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eliana Vasquez Osorio:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Andrew Jackson:** Writing – review & editing, Methodology, Conceptualization. **Charles Mayo:** Writing – review & editing, Methodology, Conceptualization. **Anja Einebærholm Aarberg:** Writing – review & editing, Data curation. **Myriam Ayadi:** Writing – review & editing, Data curation. **Francesca Belosi:** Writing – review & editing, Data curation. **Cemile Ceylan:** Writing – review & editing, Data curation. **Angela Davey:** Writing – review & editing, Methodology. **Pauline Dupuis:** Writing – review & editing, Data curation. **Julia-Claire Handley:** Writing – review & editing, Data curation. **Theresa Hemminger:** Writing – review & editing, Data curation. **Lone Hoffmann:** Writing – review & editing, Data curation. **Colin Kelly:** Writing – review & editing, Data curation. **Chrysanthi Michailidou:** Writing – review & editing, Data curation. **Sarah Muscat:** Writing – review & editing, Conceptualization. **Donna H. Murrell:** Writing – review & editing, Data curation. **Jaime Pérez-Alija:** Writing – review & editing, Data curation. **Catherine Palmer:** Writing – review & editing, Data curation. **Lorenzo Placidi:** Writing – review & editing, Data curation. **Marija Popovic:** Writing – review & editing, Methodology, Data curation. **Heidi S. Rønde:** Writing – review & editing, Data curation. **Adam Selby:** Writing – review & editing, Data curation. **Theodora Skopidou:** Writing – review & editing, Data curation. **Natasa Solomou:** Writing – review & editing, Data curation. **Joep Stroom:** Writing – review & editing, Data curation. **Christopher Thompson:** Writing – review & editing, Data curation. **Nicholas S West:** Writing – review & editing, Data curation. **Ali Zaila:** Writing – review & editing, Conceptualization. **Ane L Appelt:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Nicholas Hardcastle receives research grant funding from Varian Medical Systems and Reflexion Medical for work unrelated to the current project. Nicholas Hardcastle receives consultancy fees from SeeTreat Medical. Theresa Hemminger is an employee of Brainlab AG.].

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Appendix A. Supplementary data

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