



Original Article

Reirradiation dose constraints in clinical practice: Results of an international survey[☆]

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ABSTRACT

Introduction: Despite the increasing frequency of reirradiation (reRT) in cancer treatment, a critical lack of reliable dose constraint data remains. This study addresses this gap by collating current reRT constraints used in clinical practice across multiple centers, facilitating the development of more consistent and safer reRT guidelines.

Materials and methods: A comprehensive survey collected data on reRT patient numbers, dose constraints, sources, and dose summation methods for 30 OARs. Information also included PRV margins, tissue recovery factors (TRF) with time intervals, α/β values, near- $D_{\max}$ definitions, and dose constraints in EQD2Gy for first and reRT courses. The relative difference (X_{reRT}) between cumulative reRT and first course constraints was calculated. Constraints with data from at least 7 centers were included for further analysis.

Results: A median of 6 % of treatments in 17 participating centers were reRT. Most centers derived reRT constraints from the literature (81 %) or first course constraints (68 %). In total 209 cumulative near- $D_{\max}$ values for 19 OARs fulfilled $n \geq 7$, yielding a median inter-center variation of 21 % (IQR). While α/β values were relatively consistent, substantial variations were seen in near- $D_{\max}$ volume definition, TRF, and PRV margins. The median X_{reRT} was 26 %, primarily attributed to the TRF which had a median value of 23 %.

Conclusions: This multi-centre survey identified a concerning median inter-centre variation of 21 % in cumulative reRT dose constraints, indicating substantial heterogeneity in current clinical practices. Further prospective

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studies with rigorous and standardized dose reporting are essential to refine reRT guidelines, enhancing patient safety and treatment efficacy.

Introduction

Reirradiation (reRT), used to treat recurrent or oligometastatic disease in areas previously exposed to radiation, presents unique challenges. Determining appropriate doses to organs at risk (OARs) over multiple courses separated in time is crucial [1–12]. Cumulative dose constraints for OARs, balanced with target coverage, are incorporated at treatment planning to minimize the risk of severe toxicity. In 2019, the first single institution publication of a systematic approach to cumulative reRT dose evaluation included tabulations of constraint values, tissue recovery factors, and α/β values for 22 OARs for all treatment sites, together with detailed calculation methodologies and examples used since 2017 [13]. A subsequent consensus paper echoed findings from earlier reports and added categorizations of reRT scenarios, depending on their overlap of high dose and contributions to OARs [14].

A European Society for Radiotherapy and Oncology (ESTRO) Physics Workshop held in Lisbon in October 2022 brought together clinics and experts in reRT to discuss variability in approaches used and launch efforts to understand patterns of practice in reRT [15]. At this workshop, reRT working groups formed to provide reviews, assess clinical practices, and establish guidance for reRT. The first working group studied the variability in cumulative dose assessment in 24 clinics that were provided with a standardized set of DICOM RT files for a head & neck and a lung patient treated with reRT and instructed to use their local processes for registration and dose evaluation [16].

Our dose constraints working group was tasked with providing an overview of the current practices of multiple centres regarding reRT dose constraints. These constraints can vary based on reRT factors like the regeneration capacity of different tissues and the interval between radiotherapy courses [8]. They are also influenced by regular factors such as patient history and contraindications, the volume of normal tissue irradiated, and the fractionation regimes employed [17–20]. A key challenge in understanding reRT outcomes as they begin gradually to emerge, is understanding how individual clinics manage the practical application of dose constraints.

Consequently, our working group aimed to capture the use of real-world, clinically used reRT dose constraints; as such, it does not offer recommendations but instead provides a snapshot of current practice in the radiotherapy community using a multi-institutional survey. Though we lack high-level evidence on reRT dose constraints, this report, through the sharing of clinical data and practice, takes a necessary step towards more consistent constraints in the future.

Material/Methods

Seventeen radiotherapy departments that joined the ESTRO reRT dose constraints working group in October 2022 participated in this study. These departments ranged from those in large university hospitals treating ~ 10,000 patients per year, to smaller local centers treating ~ 1000 annually. All participating centers completed a survey regarding their reRT practice (statistics, technique, patient demographics) and sources of evidence, if any, of their adopted clinical reRT dose constraints. The full questionnaire is provided in the [supplementary materials \(SM.1\)](#). Since within one department different strategies can be applied for different OARs or circumstances, multiple answers were allowed per item, and therefore the sum of selected answers could be larger than the number of available responders.

Furthermore, participants were asked to complete a table of first course (DC_{1stRT}) and reRT cumulative dose constraints (DC_{reRT}) for 30 different OARs. Constraints were reported in equivalent dose in 2-Gy per fraction (EQD2Gy). In case where DC_{1stRT} differed between

conventional- and hypo-fractionation (roughly defined as > 5 Gy/Fx), the mean EQD2Gy value was used. ReRT specific α/β values, planning organ at risk (PRV) margins, tissue recovery factors (TRF), minimum recovery intervals, near- D_{max} definition, and dose limit type, were also collected, along with associated references. To minimise variations within centers and facilitate comparisons between all centers, only reRT patients treated using clinically accepted limits were considered, so experimental values from e.g. clinical trials were excluded.

For further analysis, we assumed an empirical relationship between first course and reRT cumulative dose constraints:

$$DC_{reRT} = DC_{1stRT} * (1 + X_{reRT}) \quad (1)$$

with X_{reRT} the relative difference between both constraints. Positive X_{reRT} -values imply that higher dose could be given with reRT due to, for example, tissue recovery. Some participating centers applied different constraints to different clinical scenarios, often related to time interval between courses. In these instances, only the highest cumulative EQD2Gy constraint was used (implying at least 12 months of recovery with maximum TRF per OAR). In this work we only considered 2 radiotherapy courses i.e. a single reRT course. We report only the cumulative reRT dose constraint data for those OARs with data from at least 7 participating centers (about 40 % response rate); this somewhat arbitrary threshold limits uncertainty while maintaining a relatively high number of OARs.

Some clinics use a consistent set of EQD2Gy DVH constraints for each OAR irrespective of the number of reRTs; for each course, they calculate the representative cumulative dose accounting for tissue recovery by incorporating TRFs [13]. Results from those clinics were recast into equation (1) as discussed in the [supplemental materials; SM.2](#) demonstrates that to account for recovery, one can equally increase dose constraints or decrease delivered dose. Furthermore, to reduce the impact of outliers, our quantitative data is summarized by medians and quartiles. Finally, this report adopts professional society based standardized nomenclatures, terminologies and reRT specific extensions [21,22].

Results

Survey on reirradiation practice

The survey results of the 17 centers are summarized in [Fig. 1](#). The median number of reRT patients treated per year by the participating centers was 100 (interquartile range [IQR] 43–238). On average, reRT accounted for a median of 6 % of all treatments (IQR 4–10 %). Estimated combinations of conventional (C) and hypo-fractionated (H) retreatments were: CC 29 %, HC 15 %, CH 32 %, and HH 24 %.

All centers used near-maximum dose estimates for cumulative constraints. Most centres (14/17) sourced constraint information from literature while others derived from first-course constraints with (10/17) or without (11/17) accounting for tissue recovery. In total, 51 different references were referred to 136 times, i.e., on average 7.2 references per OAR, varying from 2 for stomach and duodenum to 17 for heart. Eight references were mentioned at least 5 times: 5 reRT papers [13,23–26] and 3 first-course dose constraint papers [18,20,27]. Five centers also used their own clinical data. Cumulative dose-volume constraints were less frequently used: four centers did not use them at all and the majority of centers (10/17) used the first-course dose-volume constraints for reRT.

All except one center explicitly incorporated tissue recovery (TRF) for some OARs, either by correction of dose constraints (9/17) or by

modifying the planned dose from the first course (9/17). About half of the centers adjusted their reRT depending on the accuracy of available data by adjusting dose constraints (5/17) or PRV margins (4/17).

Dose summation methodologies varied, with many centers using multiple approaches. The most common method was to use one general rigid image registration (13/17). Some centers (8/17) applied separate

rigid registrations per OAR of concern and a minority (5/17) used deformable registration. Nearly half of the centers (8/17) also employed non-registration-based techniques.

Parallel OARs like lung and liver were primarily assessed using volume-based metrics (13/17). Due to the complexity of evaluating parallel structures in reRT, many centers (9/17) still relied on near-

reRT statistics	mean	SD	median	1stQ	3dQ
#patients/year	200	264	100	43	238
fraction of total (%)	7	3	6	4	10

reRT combinations	mean	SD	median	1stQ	3dQ
% CC	29	24	25	10	48
% HC	15	8	15	10	20
% CH	33	17	30	13	40
% HH	24	20	15	10	38

What are the constraint sources?	literature	1 st course constraints with recovery	our own	simply 1 st course	individual doctor decides	constraints not used
D _{max}	14	10	5	11	8	0
Dose-Volume	6	3	3	10	5	4

Is recovery used?	Yes, by correcting the planned dose	Yes, by correcting the dose constraint	Yes, only spinal cord	No
	9	9	1	1

Do constraints depend on accuracy of available data?	Yes, by adjusting PRV margins	Yes, by adjusting constraints	No	Other
	4	5	8	2

How is dose summed?	with deformable registration	with one general rigid registration	without dose registration	with one rigid registration per OAR
	5	13	8	8

What if critical dose is reached in first course?	consider a recovery factor	compromise PTV coverage	not re-treat the patient	allow a violation of the constraint
	13	14	7	8

How are parallel OARs evaluated?	not evaluated	using Dmax constraints	using Dose-Volume constraints
	2	9	13

How is reRT dose reported?	using EQD2Gy or BED dose	using physical dose
	15	9

Fig. 1. Overview of the survey results for 17 radiotherapy centers. For reirradiation combinations: C=Conventional treatment, H = hypo-fractionated treatment.

maximum cumulative dose estimates as well, despite their limitations. A large majority (15/17) reported cumulative equieffective doses using EQD2Gy or biologically equivalent dose (BED), although physical dose remained in use at some centres (9/17) to identify areas of potential increased toxicity.

When dose limits were exceeded in the first course, most centers compromised PTV coverage during reRT (14/17). Others considered applying TRF (13/17), allowed constraint violations (8/17), or, in some centers (7/17), opted not to proceed with reRT.

Dose constraint tables

Sixteen of the 17 centers supplied their dose constraints, although two did not supply first course constraints. There were no OARs with dose-volume data from at least 7 centers, so dose-volume constraints are omitted from further study. Nineteen OARs had near- $D_{\max}$ data from 7 or more centers, which yielded 209 different cumulative near- $D_{\max}$ reRT constraints and 181 first course constraints in total.

The inter-center variations in near- $D_{\max}$ definitions, recovery estimates, PRV margins, α/β , and dose limit type are depicted per OAR in box-whisker plots in Fig. 2. The overall median of maximum PRV margin was 2 mm (IQR 0–5 mm) across 188 reported margin values. The most

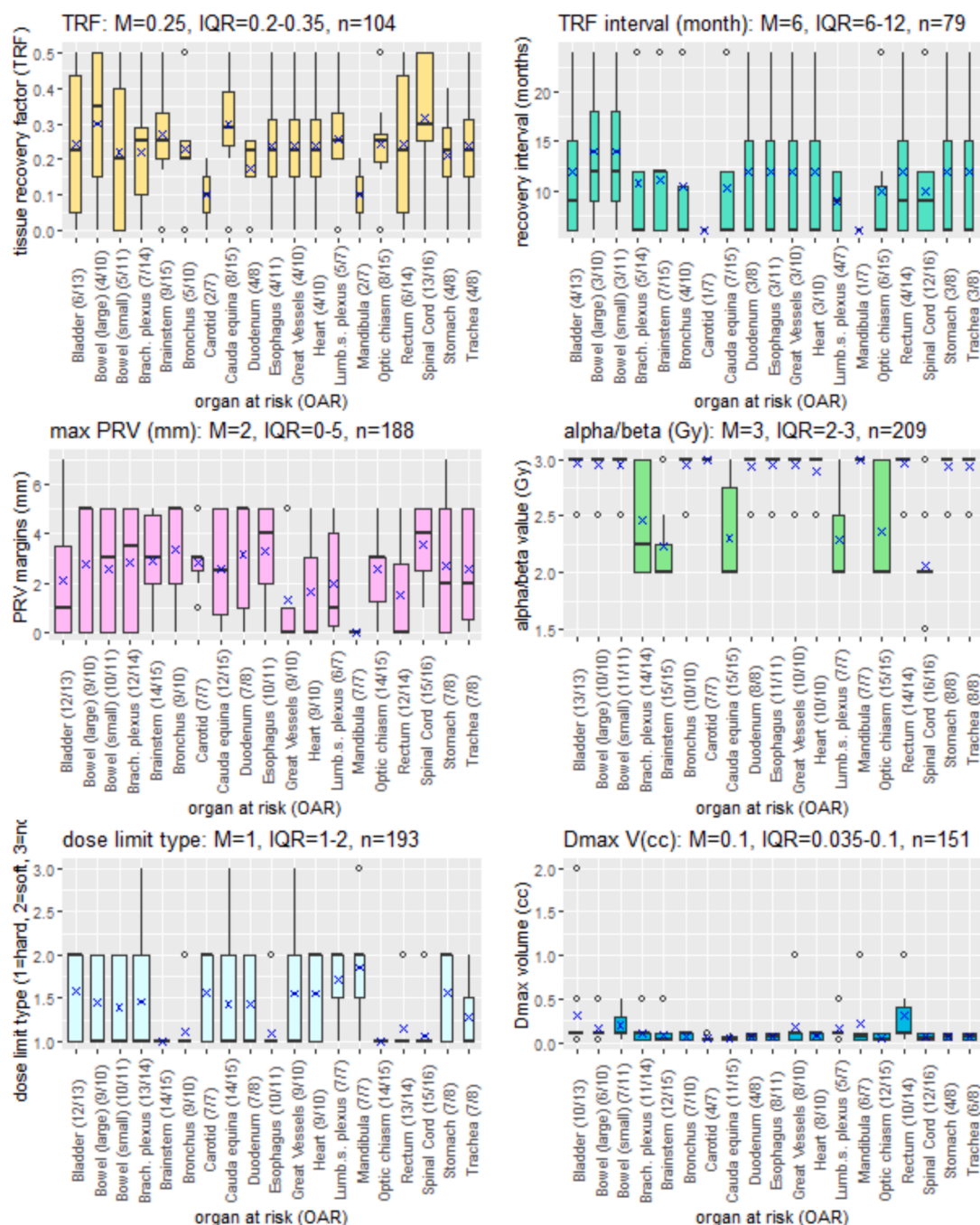


Fig. 2. Box-Whisker plots with recovery intervals, recovery factors, α/β values, PRV margins, dose limit type, and $D_{\max}$ definition used for 19 different OARs with data from at least 7 centers. Shown are the IQRs (boxes, calculated including the median), the minimum and maximum excluding outliers (whiskers), the medians (—), the means (x), and the outliers (o). Width of the boxes indicates the sample size. Number of data (n) is indicated as fraction of available OARs in the horizontal axis labels. The tile per chart contains the overall median and inter-quartile-range values and the overall number of observations.

common α/β was 3 Gy, with values 1.5–3 Gy applied to nerve structures (overall IQR 2–3, $n = 209$). The critical volumes associated with near- $D_{\max}$ constraints had a median value of 0.10 cc (IQR 0.04–0.10 cc and range 0.01–2 cc, $n = 151$). Dose constraint types were classified as 1 = hard limit (would compromise target coverage), 2 = soft limit (optimal, would not compromise target coverage), or 3 = no limit (record only), and the modal value was 1 ($n = 193$).

Quantitative tissue recovery factors were supplied for about half of the data ($n = 104$), with a median value of 25 % (IQR 20 %–35 %) and 81 values larger than zero. Non-quantitative responses (e.g. “no”, “NA”, “undefined”) were excluded. The treatment interval for these tissue recovery factors were available in 79 of 81 cases with a median of 6 months (IQR 6–12 months).

Near- $D_{\max}$ constraints for all OARs with $n \geq 7$ are summarized in a box-whisker plot (Fig. 3) and by a quantitative overview of the variation in first course and cumulative reRT near- $D_{\max}$ constraints for all OARs (Table 1). Raw data per radiotherapy center are provided in the [supplementary materials \(SM.3\)](#), showing that both the quantity of data and the inter-center variation differ significantly per OAR.

For 3 out of 16 centers, the conventional and hypo-fractionation first course constraints were consistent for all their OARs (i.e. equal EQD2Gy). For 9 centers conventional and hypo-fractionation constraints differed, so the average EQD2Gy was used. Two centers provided only one and 2 other centers provided no first course constraints. For individual centers and OARs, EQD2Gy differences between hypo- and conventional-fractionation varied from –78 % to +69 % (average 4 %, $n = 126$).

The relative inter quartile range IQR% (=IQR/median) in constraints varied from 7 % (spinal cord) to 34 % (rectum) for reRT near- $D_{\max}$, and from 3 % (trachea) to 55 % (great vessels) for first course near- $D_{\max}$. For 14 out of 19 OARs, variations were higher for reRT than for first course

radiotherapy as reflected in the median IQR% values (21 % vs 11 % respectively). In both cases the uncertainties in α/β , PRV-margin, and other factors (Fig. 2) were included in these results, i.e., no corrections were applied for these variations.

Table 1 also compares cumulative reRT constraints with first course constraints (X_{reRT} , Eq. (1)) showing median values per OAR, with first course values available in 181 of 209 cases. For spinal cord for instance, median values were 67 Gy for reRT and 50 Gy for the first course. Applying Eq. (1) for 14 of 16 spinal cord cases with $DC_{1\text{stRT}}$ available, indicated a median X_{reRT} of 33 %. Averaging over all OARs yielded a 26 % (median) increase of cumulative reRT constraints. Relative differences varied from 5 % (mandible) to 36 % (bladder) based on median values.

Discussion

This paper gives an overview of the use and values of cumulative reRT dose constraints in 17 radiotherapy centers worldwide. The results show substantial variations in current clinical practice and applied reRT constraints. Many centers had their own way of obtaining and using the constraints, TRF, dose summation, etc., likely reflecting the differences in size, experience, and research capabilities of the centers (Fig. 1). This made it very difficult to capture all practice appropriately and several rounds of quality checks were required to increase consistency in the data for this study. Nevertheless, the median IQR in reRT cumulative near- $D_{\max}$ constraints for 19 OARs is 21 % (Table 1). Furthermore, there is significant heterogeneity in important parameters like PRV margin, α/β -value, and near- $D_{\max}$ definition, which complicates the analysis and interpretation of our results. In order to better compare and learn from reRT studies, consistency and standardization in reporting is essential [22].

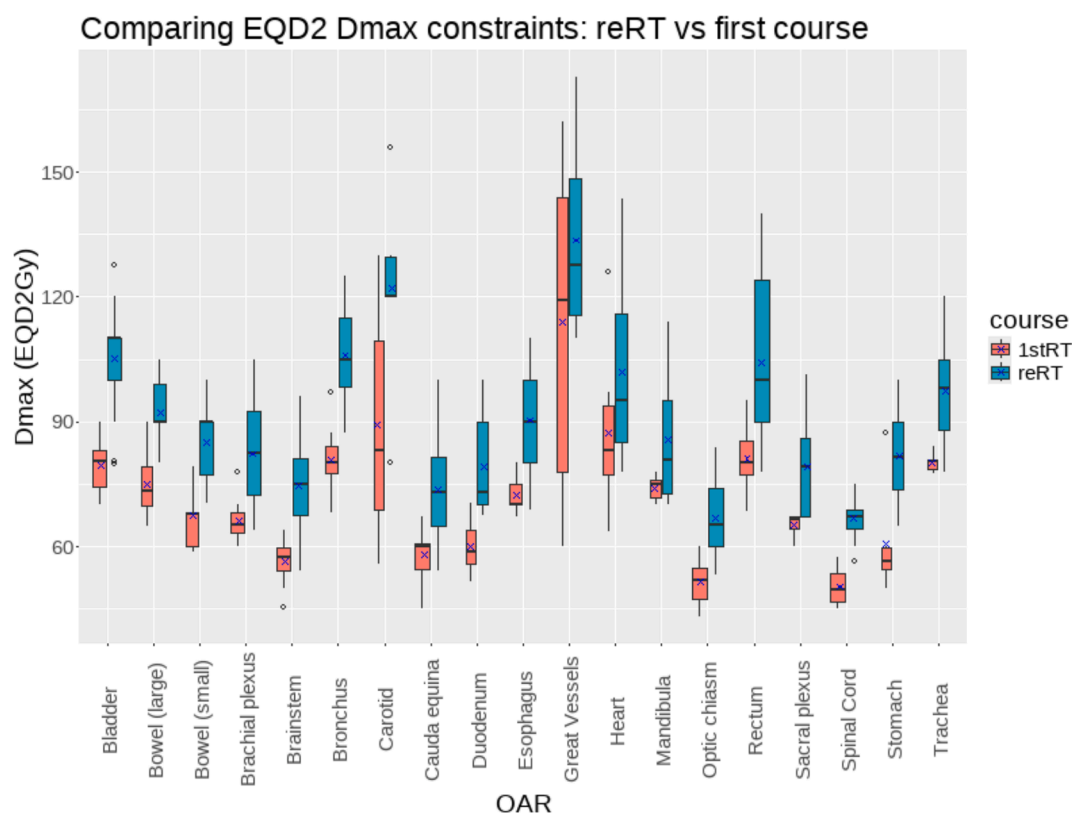


Fig. 3. Box-Whisker plot for cumulative reRT $D_{\max}$ constraints (green) in EQD2Gy of 19 different OARs with $N \geq 7$. Shown are the IQRs (boxes, calculated including the median), the minimum and maximum excluding outliers (whiskers), the medians (—), the means (x), and the outliers (o). Width of the boxes indicates the sample size. Also indicated are the corresponding 1st course dose constraints (red) from the participating centers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Overview of the variation in 1stRT and reRT near- $D_{\max}$ constraints for 19 OARs and the individual differences between cumulative reRT and 1stRT constraints for all OARs. For all values, the number of observations N has been added. Coloring indicates the size of variation (IQR) between centers (green = low, orange = high). α/β is the alpha/beta-value, PRV the maximum used PRV margin, TRF the maximum used tissue recovery factor, X_{reRT} the relative difference between cumulative reRT and 1stRT constraints (see Eq. (1)).

OAR	α/β (Gy)		PRV (mm)		TRF (%)		reRT Cum near- $D_{\max}$ (EQD2Gy)					1st course near- $D_{\max}$ (EQD2Gy)					X_{reRT} (%)		$X_{\text{reRT}} - \text{TRF}$	
	N	med.	N	med.	N	med.	N	med.	1st Q	3rd Q	IQR ₉₅	N	med.	1st Q	3rd Q	IQR ₉₅	N	med.	N	med.
Bladder	13	3	12	1	6	23%	13	110	100	110	9%	11	80	74	83	11%	11	36%	5	11%
Bowel (large)	10	3	9	5	4	35%	10	90	90	99	10%	8	73	70	79	13%	8	19%	3	0%
Bowel (small)	11	3	10	3	5	20%	11	90	77	90	14%	9	68	60	68	12%	9	20%	4	9%
Brachial plexus	14	2.3	12	3.5	7	25%	14	83	72	93	24%	13	65	63	68	7%	13	29%	6	5%
Brainstem	15	2	14	3	9	25%	15	75	68	81	18%	14	58	54	60	10%	14	32%	8	0%
Bronchus	10	3	9	5	5	20%	10	105	98	115	16%	9	80	78	84	8%	9	30%	4	12%
Carotid	7	3	7	3	2	10%	7	120	120	129	8%	7	83	69	109	49%	7	32%	2	57%
Cauda equina	15	2	12	2.5	8	29%	15	73	65	82	23%	13	60	54	61	11%	13	29%	7	2%
Duodenum	8	3	7	5	4	23%	8	73	70	90	27%	6	59	56	64	14%	6	24%	3	3%
Esophagus	11	3	10	4	4	23%	11	90	80	100	22%	9	70	70	75	7%	9	20%	3	-6%
Great Vessels	10	3	9	0	4	23%	10	128	116	149	26%	9	119	78	144	55%	9	20%	3	0%
Heart	10	3	9	0	4	23%	10	95	85	116	33%	8	83	77	94	20%	8	8%	3	0%
Sacral plexus	7	2	6	1	5	25%	7	79	67	86	24%	6	67	64	67	5%	6	27%	4	1%
Mandibula	7	3	7	0	2	10%	7	81	73	95	28%	7	75	72	76	6%	7	5%	2	-5%
Optic chiasm	15	2	14	3	8	25%	15	65	60	74	21%	14	52	47	55	14%	14	26%	7	13%
Rectum	14	3	12	0	6	23%	14	100	90	124	34%	12	80	77	85	10%	12	19%	5	17%
Spinal Cord	16	2	15	4	13	30%	16	67	64	69	7%	14	50	47	54	14%	14	33%	12	3%
Stomach	8	3	7	2	4	23%	8	82	74	90	20%	6	56	54	59	9%	6	28%	3	11%
Trachea	8	3	7	2	4	23%	8	98	88	105	17%	6	80	79	81	3%	6	24%	3	0%
median	10	3	9	3	5	23%	10	90	77	95	21%	9	70	69	75	11%	9	26%	4	3%
1st Q	8	2.1	7	1	4	23%	8	77	69	88	15%	7	59	55	62	8%	7	20%	3	0%
3d Q	14	3	12	3.8	6.5	25%	14	99	90	112	25%	13	80	76	84	14%	13	30%	5.5	11%
Sum	209		188		104		209					181					181		87	

However, first course dose constraints converted to EQD2Gy also displayed significant inter-center variations with median IQR of 11 % (Table 1). Although the great vessels and carotid artery were notable outliers, three other OARs (bladder, large bowel, spinal cord) show an $\text{IQR}_{1\text{stRT}}$ larger than IQR_{reRT} , whilst in several individual cases, first RT near- $D_{\max}$ is larger than reRT near- $D_{\max}$. This is possibly a consequence of the fact that first course RT and reRT constraints often come from different sources.

This is also apparent when comparing first course near- $D_{\max}$ constraints for conventional- and hypo-fractionation using EQD2Gy, highlighting internal inconsistencies within the first course RT constraints [28]. This reflects differences in the origins of dose constraints in the literature [17–20]. Also, some constraints evolve based on clinical feasibility rather than being robustly correlated with toxicity risk.

For 181 cases, we could compare first course constraints with cumulative reRT constraints using Eq. 1. Table 1 shows that the median of median X_{reRT} per OAR is 26 %. The TRF is the main contributor to this difference; for 87 cases with both X_{reRT} and TRF available, median of $X_{\text{reRT}} - \text{TRF} = 3$ % (Table 1). It is important to note that this 3 % might be an underestimation because non-quantitative TRF responses like “no” and “NA”, which might indicate $\text{TRF} = 0$, have been ignored, possibly overestimating median TRF. On the other hand, should first course constraints have been defined using the maximum of the normo- and hypo- first course constraints (instead of the mean), median $X_{\text{reRT}} - \text{TRF}$ would be 0 %, suggesting that the cumulative reRT constraints without recovery are generally based on these maximum values. Alternatively, the treatment being a reRT changes the status of the patient potentially

permitting a higher risk of toxicity. This would justify higher dose allowances [29], resulting in $X_{\text{reRT}} > \text{TRF}$. Several participating centers confirmed that in clinical practice risk is increased in some reRT cases, but this was not part of our survey and has not been quantified yet. Also, treatment accuracy changes [29], or the individual patient response to the first treatment, can affect the reRT dose constraints.

Adequate knowledge of TRF and e.g. changes in allowed risk for the different OARs will, on using Eq. 1, increase consistency by enabling comparisons with and facilitating the use of the better-established first-course dose constraints [17–20] in reRT treatments. For instance, this study only considered near- $D_{\max}$ constraints due to lack of readily available and accepted dose-volume constraints in reRT (even though $D_{\max}$ is technically a dose-volume constraint, as shown by the variation in $D_{\max}$ -volume in Fig. 2). Consequently we have no data for parallel OARs like lung, liver, and kidney. With trustworthy estimates for TRF and other constraint-changing factors we could derive initial approximations of reRT dose-volume constraints from existing first course RT constraints, before data from the cumbersome dose-effect studies in reRT become available for all OARs.

We had to make several simplifications to reduce the variability and complexity of the data and enable analysis. In practice, multiple intra-center constraints per OAR can be used depending on, for example, time interval, hard/soft limit and study-participation. In this paper, we asked centers to report the maximum cumulative dose constraints in reRT they would clinically allow per OAR, for patients outside clinical studies. Hence, for users of time-dependent TRF, we only considered the maximum value. Also, some centers do not increase the dose constraints

for reRT, but apply the TRF to decrease delivered doses to account for organ recovery. Both methods equate to the same delivered dose (SM.2), therefore we incorporated TRF in the cumulative constraints for consistency since many papers report cumulative reRT constraints [23–26]. Similarly, we also chose to report constraints in EQD2Gy, although BED is equally able to remove the fractionation dependency.

Similar studies on inter-center reRT constraint variation are limited. A French survey on reRT practices reported variations that appeared (not quantified) similar to ours for 6 OARs (spinal cord, bronchus, esophagus, bowel, rectum) in 9 to 27 French radiotherapy centers [30]. In the international ESTRO-EORTC survey on patterns of care for reRT, variability of cumulative dose constraints was also observed [31]. Partial tissue recovery and higher constraints were used by more than 50 % of respondents for the following organs: brain, brainstem and spinal cord, mandible, chest wall, liver, sigmoid, rectum and bladder. Inter-center constraint variation was not quantified, however, nor in any other recently published consensus document on reRT [23,24,32].

Comparing our cumulative reRT dose constraints per OAR to the median values of the 5 most referred papers in our survey [13,23–26] shows that for 11 comparable OARs (bladder, small bowel, brachial plexus, bronchus, cauda equina, esophagus, great vessels, heart, rectum, spinal cord, trachea) the mean of the constraints in those papers is 4 Gy $\pm$ 9 Gy (1SD) higher than in Table 1, showing on average more conservative practice within our centers but a large variation per OAR. Furthermore, the mean IQR of the variation in constraints in the five papers is 9 %, about half of the variation in our data.

Future work of our group will concentrate first on acquiring detailed understanding of the causes of the dose constraint differences per OAR. This will help in developing strategies to reduce the variability and increase consistency in the use and reporting of reRT dose constraints.

Conclusions

We present the first multi-centre analysis of real-world reirradiation dose constraints used in clinical practice. While shared assumptions about tissue recovery for some OARs exist, our survey of 17 centers across 13 different nations exposes a striking diversity of current practice and highlights variations; it does not represent recommendations.

In the participating centers, a median 6 % of treatments are reRT. Notably there is a 21 % inter-center variation (IQR) in reRT cumulative near-D_{max} constraints which underscores the substantial uncertainty in reRT doses.

To mitigate this and increase consistency we strongly advocate for standardized reporting practices including cumulative EQD2Gy data, α/β -values and TRF. Consistency, particularly within this complex heterogeneous patient population, will facilitate collaboration, validation of findings, and study replication, enabling cumulative progress in this field.

AI usage

No AI has been used in this research and the writing of this manuscript.

CRediT authorship contribution statement

Joep Stroom: Methodology, Writing – original draft, Data curation, Visualization, Formal analysis, Supervision, Investigation, Conceptualization. **Myriam Ayadi:** Writing – original draft, Methodology, Project administration, Data curation, Validation, Conceptualization. **Anja Aarberg:** Writing – review & editing, Data curation. **Vera Batel:** Data curation, Writing – review & editing. **Cemile Ceylan:** Data curation, Writing – review & editing. **Sinéad Cleary:** Data curation, Writing – review & editing. **Carlo Greco:** Writing – review & editing. **Lone Hoffmann:** Data curation, Validation, Writing – review & editing. **Andrew Jackson:** Conceptualization, Data curation, Writing – review &

editing. **Colin Kelly:** Data curation, Writing – review & editing. **Charles Mayo:** Writing – review & editing, Data curation, Validation, Conceptualization. **Chrysanthi Michailidou:** Writing – review & editing, Data curation. **Donna H Murrell:** Validation, Data curation, Writing – review & editing. **Sarah Muscat:** Writing – review & editing, Data curation. **Christopher JH Pagett:** Writing – review & editing, Data curation, Validation. **Kelly C Paradis:** Data curation, Validation, Writing – review & editing. **Jaime Perez-Alija:** Writing – review & editing, Data curation. **Ellen Yorke:** Writing – review & editing, Data curation, Validation. **Ali Zaila:** Data curation, Writing – review & editing. **Nick West:** Project administration, Data curation, Conceptualization, Validation, Writing – original draft, Methodology.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2025.111030>.

References

- [1] Vyfhuis MAL, Rice S, Remick J, Mossahebi S, Badiyan S, Mohindra P, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. *J Thorac Dis* 2018;10. <https://doi.org/10.21037/jtd.2017.12.50>. S2522–36.
- [2] von der Grün J, Köhn J, Loutfi-Krauss B, Blanck O, Rödel C, Balermppas P. Second infield re-irradiation with a resulting cumulative equivalent dose (EQD2max) of >180 Gy for patients with recurrent head and neck cancer. *Head Neck* 2019;41: E48–54. <https://doi.org/10.1002/hed.25428>.
- [3] Navarra P, Minniti G, Clerici E, Tomatis S, Pinzi V, Ciammella P, et al. Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. a multicenter study of the Radiation Oncology Italian Association (AIRO). *J Neurooncol* 2019;142:59–67. <https://doi.org/10.1007/s11060-018-03059-x>.
- [4] Rulach R, Hanna GG, Franks K, McAleese J, Harrow S. Re-irradiation for locally recurrent lung cancer: evidence. *Risks Benefits Clin Oncol (R Coll Radiol)* 2018;30: 101–9. <https://doi.org/10.1016/j.clon.2017.11.003>.
- [5] Nieder C, Langendijk JA, Guckenberger M, Grosu AL. Preserving the legacy of reirradiation: a narrative review of historical publications. *Adv Radiat Oncol* 2017; 2:176–82. <https://doi.org/10.1016/j.adro.2017.02.005>.
- [6] Milano MT, Mihai A, Kong F-M-S. Review of thoracic reirradiation with stereotactic body radiation therapy: a focus on toxicity risks. *Pract Radiat Oncol* 2018;8: 251–65. <https://doi.org/10.1016/j.pro.2018.01.008>.
- [7] Foster CC, Fan M, Lee NY, Yom SS, Heaton CM, Deraniyagala R, et al. Is it worth it? Consequences of definitive head and neck reirradiation. *Semin Radiat Oncol* 2020; 30:212–7. <https://doi.org/10.1016/j.semradonc.2020.02.002>.
- [8] Dörr W, Gabryś D. The principles and practice of re-irradiation in clinical oncology: an overview. *Clin Oncol (R Coll Radiol)* 2018;30:67–72. <https://doi.org/10.1016/j.clon.2017.11.014>.
- [9] Owen D, Lukovic J, Hosni A, Crane CH, Hong TS, Dawson LA, et al. Challenges in reirradiation of intrahepatic tumors. *Semin Radiat Oncol* 2020;30:242–52. <https://doi.org/10.1016/j.semradonc.2020.02.004>.
- [10] Chang DT, Koay EJ, Herman JM, Hong TS, Das P. Abdominal and pelvic reirradiation for recurrent gastrointestinal cancers. *Semin Radiat Oncol* 2020;30: 232–7. <https://doi.org/10.1016/j.semradonc.2020.02.006>.
- [11] Simone CB, Plastaras JP, Jabbour SK, Lee A, Lee NY, Choi JI, et al. Proton reirradiation: expert recommendations for reducing toxicities and offering new chances of cure in patients with challenging recurrence malignancies. *Semin Radiat Oncol* 2020;30:253–61. <https://doi.org/10.1016/j.semradonc.2020.02.007>.
- [12] Ward M, Riaz N, Caudell J, Dunlap N, Isrow D, Zakem S, et al. Refining patient selection for reirradiation of head and neck squamous carcinoma in the IMRT era: a multi-institution cohort study by the MIRI collaborative. *Int J Radiat Oncol Biol Phys* 2018;100:586–94. <https://doi.org/10.1016/j.ijrobp.2017.06.012>.
- [13] Paradis KC, Mayo C, Owen D, Spratt DE, Hearn J, Rosen B, et al. The special medical physics consult process for reirradiation patients. *Adv Radiat Oncol* 2019; 4:559–65. <https://doi.org/10.1016/j.adro.2019.05.007>.
- [14] Andratschke N, Willmann J, Appelt AL, Alaymani N, Balermppas P, Baumert BG, et al. European society for radiotherapy and oncology and European organisation for research and treatment of cancer consensus on re-irradiation: definition,

- reporting, and clinical decision making. *Lancet Oncol* 2022;23:e469–78. [https://doi.org/10.1016/S1470-2045\(22\)00447-8](https://doi.org/10.1016/S1470-2045(22)00447-8).
- [15] Vasquez Osorio E, Mayo C, Jackson A, Appelt A. Challenges of re-irradiation: a call to arms for physicists - and radiotherapy vendors. *Radiother Oncol* 2023;182: 109585. <https://doi.org/10.1016/j.radonc.2023.109585>.
- [16] Hardcastle N, Vasquez Osorio E, Jackson A, Mayo C, Aarberg AE, Ayadi M, et al. Multi-centre evaluation of variation in cumulative dose assessment in reirradiation scenarios. *Radiother Oncol* 2024;194:110184. <https://doi.org/10.1016/j.radonc.2024.110184>.
- [17] Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21: 109–22. [https://doi.org/10.1016/0360-3016\(91\)90171-y](https://doi.org/10.1016/0360-3016(91)90171-y).
- [18] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76:S10–9. <https://doi.org/10.1016/j.ijrobp.2009.07.1754>.
- [19] Grimm J, Marks LB, Jackson A, Kavanagh BD, Xue J, Yorke E. High dose per fraction, hypofractionated treatment effects in the clinic (HyTEC): an overview. *Int J Radiation Oncol* Biol* Phys* 2021;110:1–10. <https://doi.org/10.1016/j.ijrobp.2020.10.039>.
- [20] Timmerman R. A story of hypofractionation and the table on the wall. *Int J Radiat Oncol Biol Phys* 2022;112:4–21. <https://doi.org/10.1016/j.ijrobp.2021.09.027>.
- [21] Mayo CS, Moran JM, Bosch W, Xiao Y, McNutt T, Popple R, et al. American association of physicists in medicine task group 263: standardizing nomenclatures in radiation oncology. *Int J Radiat Oncol Biol Phys* 2018;100:1057–66. <https://doi.org/10.1016/j.ijrobp.2017.12.013>.
- [22] West N, Covington E, Vasquez Osorio E, Stroom J, Duchateau M, Day M, et al. Consistency in reirradiation scenarios: terminology, tissue recovery in calculations, units and reporting. *Radiother Oncol* 2024;110587. <https://doi.org/10.1016/j.radonc.2024.110587>.
- [23] Rulach R, Ball D, Chua KLM, Dahele M, De Ruyscher D, Franks K, et al. An international expert survey on the indications and practice of radical thoracic reirradiation for non-small cell lung cancer. *Adv Radiat Oncol* 2021;6:100653. <https://doi.org/10.1016/j.adro.2021.100653>.
- [24] Slevin F, Aitken K, Alongi F, Arcangeli S, Chadwick E, Chang AR, et al. An international Delphi consensus for pelvic stereotactic ablative radiotherapy re-irradiation. *Radiother Oncol* 2021;164:104–14. <https://doi.org/10.1016/j.radonc.2021.09.010>.
- [25] Abusaris H, Hoogeman M, Nuytens JJ. Re-irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. *Technol Cancer Res Treat* 2012;11:591–7. <https://doi.org/10.7785/tcrt.2012.500261>.
- [26] Hunter B, Crockett C, Faivre-Finn C, Hiley C, Salem A. Re-irradiation of recurrent non-small cell lung cancer. *Semin Radiat Oncol* 2021;31:124–32. <https://doi.org/10.1016/j.semradiol.2020.11.009>.
- [27] Diez P, Hanna GG, Aitken KL, Van As N, Carver A, Colaco RJ, et al. UK 2022 consensus on normal tissue dose-volume constraints for oligometastatic, primary lung and hepatocellular carcinoma stereotactic ablative radiotherapy. *Clin Oncol* 2022;34:288–300. <https://doi.org/10.1016/j.clon.2022.02.010>.
- [28] Stroom J, Vieira S, Greco C. 2652: improving consistency for re-irradiation dose constraints. *Radiother Oncol* 2024;194. [https://doi.org/10.1016/S0167-8140\(24\)02824-X](https://doi.org/10.1016/S0167-8140(24)02824-X). S3688–92.
- [29] Stroom JC, Vieira SC, Greco C, Nijsten SMJJG. Accuracy-dependent dose-constraints and dose-based safety margins for organs-at-risk in radiotherapy. *Phys Imaging Radiat Oncol* 2025;33:100713. <https://doi.org/10.1016/j.phro.2025.100713>.
- [30] Ayadi M, Dupuis P, Baudier T, Padovani L, Sarrut D, Sunyach M-P. Management of reirradiations: a clinical and technical overview based on a French survey. *Phys Med* 2023;109:102582. <https://doi.org/10.1016/j.ejmp.2023.102582>.
- [31] Willmann J, Appelt AL, Balermpos P, Baumert BG, De Ruyscher D, Hoyer M, et al. Re-irradiation in clinical practice: results of an international patterns of care survey within the framework of the ESTRO-EORTC E2-RADIatE platform. *Radiother Oncol* 2023;189:109947. <https://doi.org/10.1016/j.radonc.2023.109947>.
- [32] Nieder C, Willmann J, Andrasschke NH. Prospective randomized clinical studies involving reirradiation: update of a systematic review. *Strahlenther Onkol* 2023; 199:787–97. <https://doi.org/10.1007/s00066-023-02118-1>.