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Dose-Range-Dependent Voxel-Based Biological Dose Conversion From Thoracic Ultra-Hypofractionation to Conventional Fractionation: A Pilot Evaluation and Framework for Future Multicenter Studies

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Abstract

The growing use of hypofractionated radiotherapy and reirradiation has increased the need for voxel-based conversion of hypofractionated dose distributions to conventional-fractionation equivalents for organ-at-risk (OAR) dose-constraint evaluation. Some voxel-based approaches apply a uniform equivalent dose in 2 Gy fractions (EQD2) to all voxels, which may not fully reproduce the dose characteristics of conventional fractionated radiotherapy, where dose per fraction decreases below 2 Gy with increasing distance from the target. Moreover, use of voxel-based conversion approaches requires validation against established OAR dose constraints. Twelve thoracic ultra-hypofractionated treatment plans prescribed in five fractions were converted using To2GyConstraints version 1.0 (Healthy Innovations, Rachiine, Zgharta, Lebanon; www.healthy-innovations.com), a cloud-based software tool that performs dose-range-dependent voxel-based biological dose conversion from hypofractionated to conventional fractionation. It applies dose-range-dependent models: linear-quadratic-linear (LQ-L)-based EQD2 for high-dose voxels, linear-quadratic (LQ)-based EQD2 for intermediate-dose voxels, and equivalent dose in x Gy fractions (EQDx) for low-dose voxels. Original and converted dose distributions were evaluated using corresponding OAR constraints for their respective fractionation regimens. Constraint-violation status was compared using the original ultra-hypofractionated assessment as the reference. An updated standardized data-collection template incorporating thoracic OAR constraints was developed for future multicenter evaluation. The pilot evaluation demonstrated feasibility and showed promising agreement in OAR constraint-violation assessment between original and converted dose distributions. The standardized workflow provides a framework for multicenter evaluation. Dose-range-dependent voxel-based biological dose conversion using To2GyConstraints is feasible for thoracic ultra-hypofractionated radiotherapy. By accounting for radiobiological behavior across different dose ranges, this approach may improve the representation of conventional-fractionation equivalents for OAR assessment. Larger multicenter evaluation is warranted.

Categories: Radiation Oncology, Medical Physics, Healthcare Technology
Keywords: alpha/beta ratio, astro oar dose constraints, conventional fractionation, dose-range-dependent, eqd2, future multicenter studies, linear-quadratic model, thoracic ultrahypofractionation, to2gyconstraints dose converter, voxel-based biological dose conversion

Introduction

The rapid expansion of reirradiation has increased the need to accumulate previously delivered radiation dose distributions with newly planned treatments [1-3]. At the same time, the growing adoption of hypofractionated and ultrahypofractionated radiotherapy has introduced fractionation schedules that differ substantially from conventional radiotherapy, which typically delivers approximately 2 Gy per fraction [4-7]. Consequently, determining the most appropriate fractionation scheme for dose accumulation and subsequent evaluation of organ-at-risk (OAR) dose constraints has become increasingly challenging.

One practical approach is to adopt conventional fractionation as a common reference framework. Under this strategy, dose distributions from different fractionation schedules are biologically converted into their conventionally fractionated equivalents, allowing OAR evaluation using the extensive body of published conventional dose constraints derived from decades of clinical experience and numerous prospective studies [4-7]. However, the reliability of this approach depends on the accuracy with which hypofractionated dose distributions can be biologically converted to their conventional fractionation equivalents.

Although conventional LQ-based EQD2 provides a standardized framework for comparing different fractionation schedules, applying a uniform 2-Gy-per-fraction representation to every voxel in a highly

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heterogeneous ultrahypofractionated dose distribution may not fully capture the spatial dose characteristics of conventional fractionated radiotherapy. In conventional fractionation, the dose per fraction is approximately 2 Gy within the target region but generally decreases with distance beyond the target, particularly in surrounding tissues and OARs. Consequently, substantial volumes of these tissues may receive less than 2 Gy per fraction. For such low-dose regions, EQDx, where x is less than 2 Gy per fraction, may better represent the corresponding biologically equivalent dose than a uniform EQD2 representation. This distinction is particularly relevant when converted dose distributions are subsequently evaluated against conventional-fractionation OAR dose constraints. Conversely, at high doses per fraction, particularly above 7.5 Gy, the conventional LQ model may become less reliable because it may overestimate cell killing when extrapolated to this dose range. Consequently, To2GyConstraints version 1.0 (Healthy Innovations, Rachiine, Zgharta, Lebanon; www.healthy-innovations.com), a voxel-based biological dose-conversion tool, addresses these two dose-range limitations by applying EQDx to low-dose voxels and an LQ-L-based EQD2 approach to high-dose voxels, while retaining conventional LQ-based EQD2 for intermediate-dose voxels [8].

General validation of voxel-based biological dose conversion methods, particularly against established clinical OAR dose constraints, is therefore an essential step toward evaluating their clinical applicability. In this report, the feasibility of the To2GyConstraints voxel-based biological dose conversion workflow is demonstrated through a pilot study involving patients treated with thoracic ultrahypofractionated radiotherapy. Original ultrahypofractionated and biologically converted dose distributions were evaluated using published OAR dose constraints for their respective fractionation regimens, and the influence of the spatial resolution of the treatment-planning data on conversion precision was also evaluated. Building on this preliminary experience, we developed an updated standardized workflow for future multicenter evaluation, accompanied by an automated updated Excel (Microsoft Corporation, Redmond, Washington, United States) data collection template incorporating the recently published American Society for Radiation Oncology (ASTRO) 2026 OAR dose constraints [7]. Unlike To2GyConstraints version 1.0, which performs voxel-based biological dose conversion, the Excel template is designed to standardize the recording and assessment of OAR dose-constraint data derived from dose distributions converted using To2GyConstraints at participating institutions.

Technical Report

The To2GyConstraints version 1.0 dose-conversion tool was used to convert 12 thoracic ultra-hypofractionated radiotherapy plans, each prescribed in five fractions and previously generated using the Eclipse treatment planning system version 18.0 (Varian Medical Systems, Inc., Palo Alto, California, United States) with the Acuros dose-calculation algorithm, into biologically converted conventional-fractionation dose distributions.

Data were obtained from existing clinical treatment plans between March and July 2026 at the Department of Radiation Oncology, American University of Beirut Medical Center, Beirut, Lebanon. The study involved a retrospective secondary analysis of available data originally collected during routine clinical care. Before processing, the Digital Imaging and Communications in Medicine (DICOM)-Radiotherapy (RT) data were de-identified and assigned study-specific codes. Any re-identification key, if maintained by the healthcare institution, was not accessible to the investigators; therefore, the investigators could not readily ascertain the identities of the individuals represented in the research dataset. Under the United States Office for Human Research Protections (OHRP) Guidance on Coded Private Information or Biospecimens Used in Research, secondary research involving coded private information may not constitute research involving human subjects when the applicable conditions are satisfied [9].

The To2GyConstraints version 1.0 voxel-based conversion methodology has been described in detail previously [8]. Briefly, the converter uses linear quadratic (LQ)-based EQD2 for voxel doses per fraction below 7.5 Gy and linear-quadratic-linear (LQ-L)-based EQD2 for higher doses. A fixed dose-per-fraction threshold is defined as the mean of the prescription dose per fraction and 2 Gy. For voxels with doses per fraction below this threshold, EQDx is calculated, where x represents the biologically equivalent dose per fraction.

For the pilot evaluation, OAR dose constraints for 5-fraction regimens from the Timmerman 2021 study [4] and the RecoRad 2025 studies [5,6] were used. The α/β ratio is a tissue-specific radiobiological parameter in the LQ and LQ-L models that characterizes sensitivity to dose per fraction and is expressed in Gy. A broad range of α/β values has been reported for normal tissues and organs [10-13]. A single commonly used α/β value was selected for each OAR for which constraints were available for both regimens: 2 Gy for the brachial plexus, spinal cord, and medulla; 2.5 Gy for the great vessels and heart; 3 Gy for the esophagus and lungs; and 3.5 Gy for the trachea and large bronchi. Dose-constraint assessments focused on OARs in which a dose-constraint violation (DCV) was identified in either the original ultra-hypofractionated or To2GyConstraints-converted dose distribution. In addition, to evaluate the influence of treatment-planning data spatial resolution on conversion precision, the computed tomography (CT) slice thickness, CT pixel spacing, and dose grid size were collected for each patient. For OARs containing at least one voxel with a dose per fraction greater than the fixed dose-per-fraction threshold, the maximum dose (Dmax) calculated by To2GyConstraints was compared with the theoretical Dmax calculated manually.

Building on the pilot evaluation, a standardized workflow was developed to facilitate future multicenter evaluation of voxel-based biological dose conversion across a larger international cohort. The workflow incorporates the recently published ASTRO 2026 OAR dose constraints [7] and provides a standardized data-collection template for participating centers. The template records the participating center, patient number, treatment planning system (TPS) and version, thoracic site, treatment category defined as stereotactic body radiation therapy (SBRT) or ultra-hypofractionation not classified as SBRT, CT slice thickness, dose grid size, prescription dose, number of fractions, dose per fraction, dose-conversion software and version, OAR, tissue-specific α/β value, dose-volume histogram (DVH) metric, and constraint type. The OARs and corresponding DVH metrics were selected from the ASTRO 2026 consensus recommendations based on the availability of constraints for both thoracic 5-fraction ultra-hypofractionated and conventional fractionation regimens. Users enter the measured values from the original ultra-hypofractionated and converted dose distributions, and the corresponding DCV status is automatically determined by comparing each value with the applicable constraint. The DCV status of the original ultra-hypofractionated dose distribution is used as the reference classification. The comparison outcome is automatically calculated from the two DCV statuses and color-coded as true positive, true negative, false positive, or false negative.

To facilitate standardized and secure preparation and transfer of DICOM data for To2GyConstraints dose conversion, AnonyConverter (Healthy Innovations) was developed as a locally installed application. The application automates the workflow, including local anonymization of DICOM-RT files before cloud-based processing, file compression and upload to the conversion service, access to the corresponding web interface for α/β value entry, download and extraction of the processed files, and local restoration of the original patient identifiers. In addition to local anonymization, data transferred between the user and the cloud-based service are protected by encrypted communication. Patient files are automatically deleted from the cloud-based service within a maximum of five days, allowing sufficient time for users to retrieve the converted files when needed.

For illustrative purposes in the present report, a separate thoracic ultra-hypofractionated treatment plan, not included in the 12-patient pilot cohort, generated using the Monaco TPS version 5.11.03 (Elekta AB, Stockholm, Sweden), was converted according to the proposed workflow. The original and resulting converted dose distributions were then visualized to highlight the different dose regions corresponding to the LQ, LQ-L, and EQDx conversion approaches.

DCVs were observed for three OARs in three patients (Table *1*): the esophagus (V14Gy = 8.1 mL in the original ultra-hypofractionated dose distribution and Dmax = 60.2 Gy in the To2GyConstraints-converted distribution), great vessels (Dmax = 53.1 Gy and 144.0 Gy, respectively), and heart (Dmax = 47.3 Gy and 116.1 Gy, respectively). For the esophagus, no DCV was identified in either the original ultra-hypofractionated distribution according to the Timmerman 5-fraction constraints or the converted distribution according to the RecoRad conventional-fractionation constraints. Similarly, no DCV was identified for the great vessels or heart in the converted distributions; however, RecoRad conventional-fractionation recommendations do not provide Dmax constraints for these OARs, precluding direct comparison of this metric.

Patient #	OAR	Timmerman 2021 [4]		RECORAD 2025 [5, 6]	
		Hypofractionnation	To2GyConstraints V1.0	Hypofractionnation	To2GyConstraints V1.0
5	Esophagus	Dmax=31.99Gy (<38Gy)[n]	Dmax=60.15Gy (>60Gy)[d]	Dmax=31.99Gy (<35Gy)[n]	Dmax=60.15Gy (<69Gy)[n]
5	Esophagus	V32.5Gy=0.00cc (<5cc)[n]	V51Gy=0.29cc (<5cc)[n]	V14Gy=8.10mL (>2mL)[d], V27.5Gy=0.80mL (<5mL)[n] & V32.5Gy=0.00mL (<5mL)[n]	V60Gy=0.00% (<30%)[n] & V50Gy=1.14% (35%)[n]
11	Great vessels	Dmax=53.09Gy (>53Gy)[d]	Dmax=143.97Gy (>76Gy)[d]	Dmax=53.09Gy (>53Gy)[d]	No Dmax OAR constraints available
12	Heart	Dmax=47.27Gy (>38Gy)[d] & V32Gy=1.97cc (<15cc)[n]	Dmax=116.07Gy (>68Gy)[d]	Dmax=47.27Gy (>38Gy)[d]	No Dmax OAR constraints available

TABLE 1: Patients and OARs with at least one detected dose-constraint violation among the 12 patients

Results are shown for Timmerman 2021 5-fraction constraints [4] applied to the original hypofractionated dosimetry, and for normofractionated Timmerman 2021 constraints applied to the dosimetry converted using the To2GyConstraints converter. The same analysis is performed for RECORAD 2025 5-fraction constraints [5,6] applied to the original hypofractionated dosimetry, and for normofractionated RECORAD 2025 constraints applied to the To2GyConstraints-converted dosimetry. Direct comparisons between the Timmerman 2021 and RecoRad 2025 frameworks are limited by differences in the available dose constraints. In particular, direct Dmax comparisons for the great vessels and heart are not possible because the RecoRad 2025 recommendations do not provide corresponding Dmax constraints.

d = detection of OAR constraint violation; n = no detection of OAR constraint violation, although detected elsewhere.

VxGy: volume of organ receiving at least x Gy; Dmax: maximum dose; OAR: organ-at-risk

Table 2 shows the influence of the spatial resolution of the treatment-planning data on conversion precision. Five Dmax values calculated automatically by To2GyConstraints were compared with their corresponding theoretical values calculated manually. All differences from the manual calculations were less than 5%. The largest absolute difference was 4.34%, with a signed difference of −4.34%, corresponding to the largest dose grid size used (2.5 mm). In contrast, the smallest difference was +0.03%, corresponding to the smallest dose grid size used (1.25 mm).

Patient #	CT Slice Thickness (mm)	CT Pixel Spacing (mm)	Dose Grid Size (mm)	OAR	α/β (Gy)	Prescribed Dose per Fraction (Gy)	Fixed Dose-per-Fraction Threshold (Gy)	Original Plan Dmax (Gy)	EQD2 Model Used	Manual EQD2 Calculation (Gy)	Calculated by To2GyConstraints v1.0 (Gy)	Difference from Manual Calculation (%)
4	3	0.98	2.5	Great vessels	2.5	10	6	33.27	LQ	67.68	66.53	-1.70
5	1.5	0.89	1.5	Esophagus	3	7	4.5	31.99	LQ	60.13	60.15	+0.03
5	1.5	0.89	1.5	Trachea and large bronchus	3.5	7	4.5	22.83	LQ	33.48	34.75	+3.79
11	3	0.95	1.25	Great vessels	2.5	10	6	53.09	LQ-L	143.96	143.97	+0.01
12	1.5	0.81	2.5	Heart	2.5	10	6	47.27	LQ-L	121.33	116.07	-4.34

TABLE 2: Comparison of Dmax values obtained by manual EQD2 calculation and To2GyConstraints v1.0 for voxels above the fixed dose-per-fraction threshold, with corresponding CT and dose-grid characteristics.

All patients received five fractions. Only patients with at least one OAR containing a voxel with a dose per fraction greater than the fixed dose-per-fraction threshold were included. The fixed dose-per-fraction threshold was calculated as the mean of the prescribed dose per fraction and 2 Gy. The "EQD2 Model Used" column indicates the model applied to the corresponding voxel: the LQ model for voxel doses per fraction <7.5 Gy and the LQ-L model for voxel doses per fraction >7.5 Gy. CT slice thickness, CT pixel spacing, and dose-grid size are reported to characterize the spatial resolution of the treatment-planning data. The percentage difference was calculated as $\frac{\text{To2GyConstraints v1.0} - \text{manual EQD2}}{\text{manual EQD2}} \times 100$

EQD2: equivalent dose in 2 Gy fractions; OAR: organ-at-risk

An updated standardized Excel-based template was developed for future multicenter evaluation of voxel-based biological dose conversion based on the ASTRO 2026 thoracic OAR dose constraints. Only five OARs with corresponding constraints for both fractionation regimens were identified: brachial plexus, esophagus, heart, lungs, and spinal canal. The automated, color-coded Excel version of the template can be downloaded from the Appendices.

Figure *1* illustrates the original ultra-hypofractionated and corresponding To2GyConstraints-converted dose distributions for a 50 Gy in 5-fraction lung treatment plan. The converted distribution demonstrates a broader spatial extent of the 100% dose region, with the corresponding dose extending further into the surrounding healthy lung tissue than in the original ultra-hypofractionated distribution. This apparent expansion reflects the biological dose conversion and the lower α/β value assigned to healthy lung tissue (α/β = 3 Gy) compared with the tumor (α/β = 10 Gy), resulting in a greater biologically converted dose for the same physical dose in lung tissue. Figure *1* also visually demonstrates the distinct regions in which the LQ-L-based EQD2, conventional LQ-based EQD2, and EQDx approaches were applied.

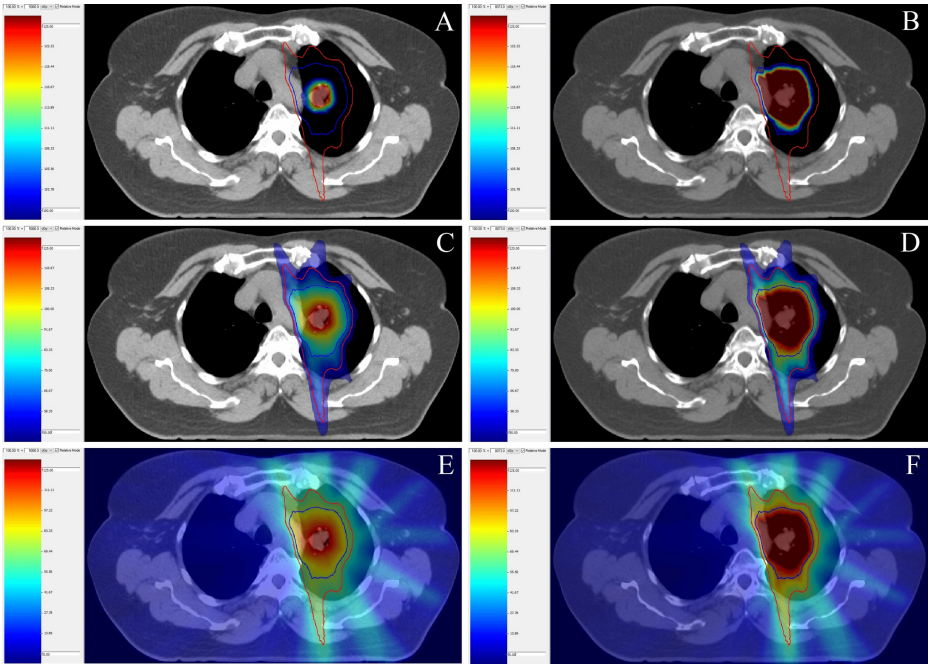


FIGURE 1: Dose distributions for an ultra-hypofractionated left lung tumor radiotherapy plan and the corresponding biologically converted dose distributions on an axial CT slice traversing the tumor.

A, C, and E: original ultra-hypofractionated dose distribution for a prescription of 50 Gy in 5 fractions.

B, D, and F: corresponding dose distributions obtained using the To2GyConstraints converter.

The color-wash color bar represents the dose distribution displayed on the CT images. The 100% color-wash dose level was set to 50 Gy on the left (A, C, and E), representing the original ultra-hypofractionated dose distribution, and to 80.73 Gy on the right (B, D, and F), representing the dose distribution converted using To2GyConstraints and corresponding to the LQ-L EQD2 for the tumor (α/β = 10 Gy). In all images, the maximum display threshold was set to 125%, while the minimum thresholds were set to 100%, 50%, and 0% for the upper (A and B), middle (C and D), and lower (E and F) images, respectively. The blue isodose line represents the 7.5 Gy-per-fraction voxel dose level, whereas the red isodose line represents the 6 Gy-per-fraction fixed threshold. Accordingly, voxels inside the blue isodose line were converted using the LQ-L-based EQD2 approach, voxels between the blue and red isodose lines were converted using conventional EQD2 based on the LQ model, and voxels outside the red isodose line were converted using the EQDx approach.

LQ-L: linear-quadratic-linear; EQD2: equivalent dose in 2 Gy fractions; EQDx: equivalent dose in x Gy fractions

Discussion

In this 12-patient pilot study, To2GyConstraints generated biologically converted conventional-fractionation dose distributions with promising agreement in OAR dose-constraint violation assessment with the original ultrahypofractionated distributions. In addition, the results demonstrated that the spatial resolution of the treatment-planning data can affect dose-conversion precision, highlighting the importance of considering CT slice thickness, CT pixel spacing, and dose grid size when performing voxel-based dose conversion. Although these preliminary findings require validation in a larger cohort, they support the feasibility of the proposed voxel-based conversion workflow. The recently published ASTRO 2026 consensus OAR dose constraints provide a standardized framework for the planned multicenter evaluation.

Despite these preliminary findings, the descriptive analysis of 12 patients, including only three patients with OAR DCVs, is insufficient to establish the clinical validity or reliability of the proposed conversion approach or to demonstrate dosimetric equivalence. The limited number of observed violations also restricts the interpretation of classification performance and the precision of any corresponding estimates. Accordingly, the planned multicenter evaluation should be designed around clearly defined primary endpoints, a sample-size calculation conducted before data collection, and a prespecified statistical analysis plan that defines appropriate statistical methods and uncertainty estimates.

Because the proposed dose-conversion software is a low-cost, web-based tool, it would be widely accessible to a large range of radiotherapy centers, particularly those with limited resources. In the present study, the dose converter was demonstrated to be compatible with Eclipse and Monaco, the two most widely used TPS

for SBRT worldwide [14], supporting the potential portability of the workflow across different TPS environments.

For the standardized multicenter workflow, predefined tissue-specific α/β values were assigned to each OAR and fixed to the same values used in the pilot study to ensure consistency across participating centers, minimize methodological variability, and provide a common starting point for multicenter evaluation. However, these values should not be interpreted as definitive or necessarily optimal estimates for the corresponding tissues. Future studies should investigate the effects of varying α/β values on converted dose distributions and the resulting OAR dose-constraint classifications. In addition, although the dose-calculation algorithm does not directly enter the mathematical conversion process, the accuracy of the converted dose distribution depends on the accuracy of the original dose distribution generated by the treatment-planning system, as well as on the spatial resolution of the input data.

Following validation of the converter for OARs with commonly accepted α/β values, as well as further validation in anatomical sites beyond the thorax, a potential future application would be to investigate tissues for which the α/β value remains uncertain but clinically validated OAR dose constraints are available for different fractionation schedules. By applying a validated voxel-based conversion framework to dose distributions from different fractionation regimens and comparing the resulting dose-constraint classifications, it may be possible to estimate tissue-specific α/β values. Conversely, when a tissue-specific α/β value is available, but OAR dose constraints are incomplete or unavailable for a particular fractionation schedule, the same framework could potentially be used to investigate or estimate corresponding dose constraints by biologically converting dose distributions between fractionation regimens.

Conclusions

This pilot study demonstrates the feasibility of voxel-based biological dose conversion using To2GyConstraints for thoracic ultrahypofractionated radiotherapy. The spatial resolution of the treatment-planning data, particularly the dose grid size, should be considered because it can affect dose-conversion precision. However, the small sample size and limited number of observed OAR dose-constraint violations limit the scope of the analyses and the generalizability of these preliminary findings, which do not establish the clinical validity or reliability of the proposed approach. Further multicenter evaluation using the elaborated standardized workflow and the updated, automated Excel data-collection template based on ASTRO 2026 OAR dose constraints is warranted.

Collecting data from a larger number of patients and institutions may provide a broader range of OAR dose-constraint violations, enabling more comprehensive statistical analyses. Future studies could assess the converter's classification performance using true-positive, true-negative, false-positive, and false-negative results, as well as relevant metrics such as accuracy, precision, sensitivity, and specificity. Furthermore, comparative studies of To2GyConstraints and Conventional EQD2, both available within the same cloud platform, would be valuable for identifying cases in which their dose-conversion results differ and determining whether these differences offer meaningful advantages for OAR dose-constraint assessment. Future studies should also incorporate sensitivity analyses addressing uncertainty in tissue-specific α/β values and assess the robustness of dose conversion across different treatment-planning systems and spatial resolutions. These investigations would provide further evidence regarding the reliability and limitations of To2GyConstraints and help clarify its contribution to OAR dose-constraint assessment in support of clinical practice.

Appendices

The automated, color-coded Excel version of the template can be downloaded from the following link: https://sub-domain.healthy-innovations.com/download-SupplementaryTable3CureusThorax5Fr-page

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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