RadOnc: An R Package for Analysis of Dose-Volume Histogram and Three-Dimensional Structural Data

Software

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Abstract: **Purpose/Objectives**: Dose volume histogram (DVH) data are generally analyzed within the context of a treatment planning system (TPS) on a per-patient basis, with evaluation of single-plan or comparative dose distributions. However, TPS software generally cannot perform simultaneous comparative dosimetry among a cohort of patients. The same limitations apply to parallel analyses of three-dimensional structures and other clinical data.

Materials/Methods: We developed a suite of tools ("RadOnc" package) using R statistical software to better compare pooled DVH data and empower analysis of structure data and clinical correlates. Representative patient data were identified among previously analyzed adult (n=13) and pediatric (n=1) cohorts and these data were used to demonstrate the performance and functionality of the RadOnc package.

Results: The RadOnc package facilitates DVH data import from the TPS and includes automated methods for DVH visualization, dosimetric parameter extraction, statistical comparison among multiple DVHs, basic three-dimensional structural processing, and visualization tools to enable customizable production of publication-quality images.

Conclusions: The RadOnc package provides a potent clinical research tool with the ability to integrate robust statistical software and dosimetric data from cohorts of patients. It is made freely available to the community for their current use and remains under active development.

1. Introduction

Modern radiotherapy techniques depend increasingly on detailed volumetric imaging and are associated with an ever increasing degree of complexity. These techniques (e.g. 3D conformal, intensity-modulated, image-guided, stereotactic, particle-based) are all predicated upon an in-depth understanding of dose distributions, tumor responses, and normal tissue complication probabilities. As such, radiation treatment planning and overall plan evaluation make heavy use of dose volume histogram (DVH) data, which provides a mathematical framework for

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per-target/organ dose summarization and analysis. DVHs represent the frequency distribution of doses over a given volume composed of 3D voxels and have been used routinely to guide clinical care [1].

DVH data are generally analyzed within the context of a treatment planning system (TPS) on a per-patient basis, with evaluation of single-plan or comparative dose distributions. Meticulous structure-by-structure review is performed on this data during initial and/or iterative plan evaluation and quality assessment (per physician prescription and treatment goals), with application of structure-specific dose constraints. However, correlation of dosimetric data with clinical information located outside of the TPS (e.g. treatment response or follow-up toxicity) remains a significant hurdle for many clinical and research-related inquiries. Moreover, TPS software is generally unable to perform comparative dosimetry simultaneously among a cohort of patients.

Such analyses instead necessitate dosimetric data export from the TPS itself. Both commercially-available and institution-specific TPSs are generally capable of this export, which may be implemented in many formats. The standard format is a radiotherapy-specific extension of the Digital Imaging and Communications in Medicine (DICOM) format, DICOM-RT, which can store dosimetric and treatment plan data as well as structural information and any associated images [2]. However, the DICOM-RT format is implemented inconsistently across vendors, and subsequent analysis requires one or more additional software tools for data import and interpretation.

Many diverse platforms exist for such analyses. For instance, dicompyler presents an open-source Python-based tool for DICOM import, visualization, and dose analysis [3]. SlicerRT is an open-source radiotherapy extension of 3D Slicer with advanced DICOM analysis and imaging functionality [4]. HART on the other hand is a MATLAB-based suite emphasizing DVH visualization and analysis [5]. These and other available software tools each have their own strengths as well as their own shortcomings (e.g. dependency on commercial closed-source software packages such as MATLAB).

The suite of tools described herein was designed to facilitate DVH and three-dimensional data import (initially from Varian's Eclipse TPS, but ultimately extensible to any TPS) and subsequent analysis. These tools include methods for DVH visualization, dosimetric parameter extraction, statistical comparison among multiple DVHs, and rudimentary three-dimensional structural processing. Each tool will be discussed in further detail within the context of this manuscript, however additional documentation is provided directly within the RadOnc package download (freely available on CRAN [6]). Note that this software was created specifically for the R statistical package and thus enables free access to these tools across multiple computing platforms [7].

2.   Methods and Materials

2.1.   Software

The RADONC package was designed and authored by R.F.T. using R version 3.0.2 for Mac OS X [7]. The software introduces new class types for storing and processing DVH and three-dimensional structure data and implements and extends S4 methods for flexible analysis. A graphical depiction of these data types and their relationships is shown in Figure 1.
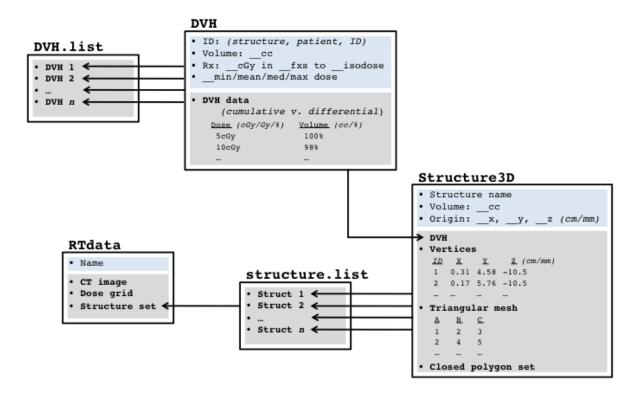

Figure 1: RADONC **package class structures and their relationships.** Five novel class structures utilized by the RADONC package for data analysis are shown in black boxes with overlying labels. Rudimentary data descriptors are contained within each class box (bulleted lists) and arrows indicate the dependence of one class upon another.

The software depends upon the availability of multiple other packages including "graphics", "grDevices", "methods", "rgl" (which itself depends on the availability of X11 library for Mac OS X), "geometry", "oro.dicom", and "ptinpoly". The RADONC package source code as well as compiled versions – for Mac OS X, Windows, and Linux – are uploaded to and maintained on the Comprehensive R Archive Network (CRAN) repository, adherent to CRAN specifications and requirements [8].

All analyses and images presented herein were generated exclusively using the RADONC package (v. 1.0.8) and the available clinical data (described below).

2.2. DVH analysis

The RADONC package makes general use of two forms of DVHs. One is called a "differential" DVH, where volume is defined as the absolute or relative proportion of a structure that receives no more or less than a given dose. The other form ("cumulative" DVH) defines volume as the absolute or relative proportion of a structure that receives at least a given dose. In a cumulative DVH, 100% of the volume receives at least 0cGy dose, and 0% of the volume receives any dose that exceeds the structure maximum dose.

The RADONC package is capable of import of TPS-calculated DVH data (currently supported for Eclipse and CadPlan [legacy] formats). The package can also be used to import and process the industry-standard DICOM-RT format, enabling independent calculation of DVHs given a pre-specified dose grid and one or more structure sets. These DVH calculations are performed as a trilinear interpolation of the dose grid at regular intervals, dividing the bounding box for each structure into a series of uniform voxels as previously described [9].

While DVHs generally describe total dose statistics, the biological effects of a given dose depend significantly on dose fractionation. Two identical DVH curves may in fact represent two widely divergent treatments if, for instance, one patient is treated to 6000cGy in four 1500cGy fractions whereas another is treated to 6000cGy in thirty 200cGy fractions. Linear quadratic extrapolation (LQE) has been used to model biologically iso-effective doses [10] and is implemented within the RADONC package for conversion of and comparison among DVHs accounting for varying dose fractionation.

Additionally, dose may be summarized by single parameters, calculated from the full DVH. For instance, integral dose represents the volume integral of dose deposited in a structure, mathematically determined as the area under the curve of the corresponding differential dose absolute volume histogram. The RADONC package allows calculation of integral dose over an arbitrary range of doses, thus the integral of dose to PTV>100% can be computed. As a fraction of total integral dose, this value is equivalent to the percent volume receiving at least 100% of the prescribed dose.

Whereas integral dose treats all portions of the DVH with equal weight, the generalized equivalent uniform dose (gEUD) is calculated as a biologically-weighted value which may vary according to tissue-specific parameters. The gEUD is interpreted as a single dose which, when distributed evenly throughout the structure volume, is iso-effective with the heterogeneously distributed dose represented by the DVH [11].

2.3. Three-dimensional structure analysis

The RADONC package enables import of three-dimensional structural information (e.g. DICOM-RT structure set and dose grid data) from the TPS. Axially-segmented DVHs may be calculated from the corresponding dose

grid (e.g. according to the Advanced Technology Consortium – ATC – method [9]).

Pairwise analysis of volumetric structure overlap can be determined by such metrics as the Dice similiarity coefficient (DSC) [12] and the Hausdorff distance (dH) [13], both of which are implemented in the current version of the RADONC package, according to equations (1) and (2), respectively:

$$DSC = 2 \times \frac{V_1 \cap V_2}{V_1 + V_2} \tag{1}$$

$$d_H(X,Y) = \max\left\{ \sup_{x \in X} \inf_{y \in Y} d(x,y), \sup_{y \in Y} \inf_{x \in X} d(x,y) \right\} \tag{2}$$

2.4. Clinical Data

Representative clinical patient data were identified among previously analyzed adult and pediatric cohorts (all data were obtained with institutional review board approval). One randomly chosen adult female ("Jane Doe") was identified among a cohort of patients with unresectable pancreatic cancer. This patient was treated with definitive chemoradiation to a prescription dose of 5500cGy delivered in 25 daily 220cGy fractions. This example dataset was exported from Varian's Eclipse TPS as a table of individual DVH values calculated to 5cGy resolution. Groupwise DVH analysis incorporated data from an additional 12 patients in the unresectable pancreas cohort, with export of tabular DVH data at 5cGy resolution in all cases. DICOM-RT data was also exported for patient Jane Doe to enable independent DVH calculation from dose grid information as well as calculation of axially-segmented DVH data.

Independently, volumetric data from a separate study investigating inter-observer variability in the delineation of dentition was exported for a single representative pediatric patient. In the data presented here, the same structures (i.e. individual teeth) were delineated independently by three clinicians. This data was exported from the TPS in DICOM-RT format.

3.   Results

3.1. DVH data import and calculation

Individual DVHs were exported from Varian's Eclipse TPS for a single representative patient with unresectable pancreas cancer, treated with definitive chemoradiation to a prescription dose of 5500cGy. Each DVH was imported as a differential DVH. An example of two differential DVHs (bilateral kidneys) from this patient are shown in Figure 2A. On the other hand, DVHs are more commonly displayed as cumulative graphs (Figure

2B). In this example depicted in Figure 2, the RADONC package was used to automatically convert between differential and cumulative DVH formats, and to generate DVH graphs accordingly. While most commercial TPSs are able to perform such computations individually, they are generally unable to replicate these calculations automatically across patient cohorts.

Note that the DVHs from multiple non-overlapping structures may also be combined by direct summation of differential DVHs. Using the RADONC package, total kidney dose was calculated from individual left and right kidney DVHs (Figure 2).
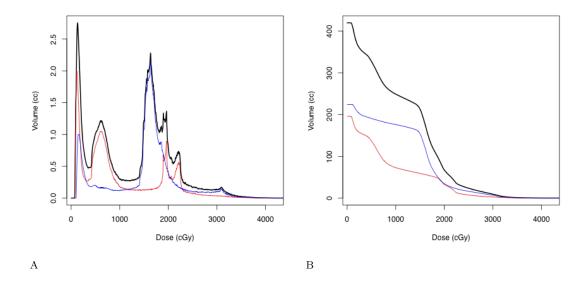

A   B

Figure 2: **Differential and cumulative kidney DVHs.** (A) Differential DVHs are displayed for individual left and right kidneys (red/blue) as well as total calculated kidney dose (black). (B) Cumulative DVHs are similarly displayed for individual left and right kidneys (red/blue) as well as total calculated kidney dose (black). Note that individual kidney differential DVH data was directly exported from the TPS for a single patient with pancreatic cancer; all other data was calculated using the RADONC package.

While it is generally sufficient to analyze TPS-calculated DVH data, integration of DVH information across multiple different platforms (e.g. in the context of a multi-institutional clinical trial) best relies upon centralized DVH calculation using a single analytical tool [14]. The RADONC package is able to perform such analysis and was therefore used to recalculate DVH from dose grid data for the same patient as above (Figure 3). Overall, these calculations demonstrate a high degree of concordance with TPS-derived DVH values (99.8 ± 0.2% agreement), and are increasingly accurate with smaller calculation voxel sizes (data not shown). Correspondingly, there is decreased accuracy among DVH calculation algorithms (e.g. ATC) for smaller structures, generally limited by voxel resolution [9].
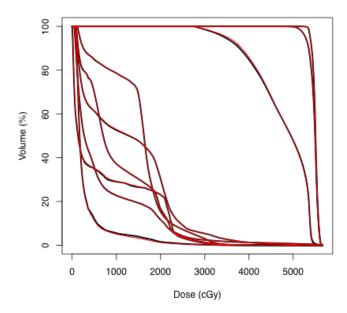
Figure 3: **Comparison of TPS exported and RadOnc package calculated DVHs.** TPS exported DVH data and corresponding DVH data calculated independently by the RADONC package from dose grid information are shown for each of nine structures (red and black curves, respectively).

3.2. DVH comparisons

One of the main challenges for dosimetric analysis is the inability to compare DVHs among multiple plans (i.e. different volumetric imaging data sets pertaining to one or more patients). Such combined analyses require centralized or simultaneous access to all relevant data. Using the RADONC package, multiple DVHs may be imported at the same time and can thus be compared to one another directly, accounting for varying prescription doses as necessary. An example of this is shown for a group of 39 separate DVHs, each representing dose to the same structures (duodenum and clinical target volume [CTV]) extracted from different treatment plans (Figures 4A and 4B). Note that in Figure 4, prescription dose was identical in all cases.

DVHs can be analyzed in group-wise fashion to generate statistical distributions and parameters such as standard deviation and interquartile range, which can be depicted graphically as shown in Figures 4C and 4D. Furthermore, groups of DVHs may be compared by standard statistical tests such as t-test and Wilcoxon rank sum test, enabling parallel quantitative assessment of numerous dosimetric parameters simultaneously (Figures 4E and 4F).

DVHs can also be summarized by single dosimetric parameters for comparison as required. For instance, integral dose represents the volume integral (total dose) deposited in a structure. Integral dose fractions calculated using
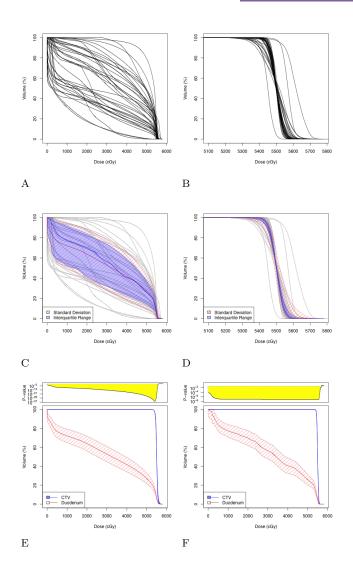
Figure 4: **Groupwise characterization and inter-group comparison of DVHs for two different structures.**
(A) Cumulative DVHs are shown for duodenum from three different treatment plans calculated for each of 13 different patients (n=39). (B) Cumulative DVHs are shown for corresponding CTV (n=39). (C) Individual duodenum DVHs are shown in grey, with mean and median DVHs in red and blue, respectively. Groupwise standard deviation about the mean and interquartile range are shown in red and blue shaded regions, respectively. (D) The individual and groupwise data are shown for CTV as in panel (C). (E) Inter-group comparison by two-tailed t-test of duodenum and CTV data with groupwise means shown in the lower portion of the panel (red and blue, respectively). The 95% confidence intervals are shown as shaded regions about the mean DVHs. Statistical significance (p-values) is shown on an inverse logarithmic scale in the upper panel, with yellow highlights representing statistically significant intervals. (F) Inter-group comparison by Wilcoxon rank-sum test of duodenum and CTV data, depicted in analogous fashion to panel (E).

the RadOnc package are approximately equivalent to doses extracted directly from the DVH (median tolerance $\pm$ 0.001% for PTV). Calculation of gEUD parameters are also implemented within the RadOnc package, with example functionality shown in Figure 5; gEUD is shown as a function of tissue specific parameter for both tumor ("Target") and two neighboring OARs.
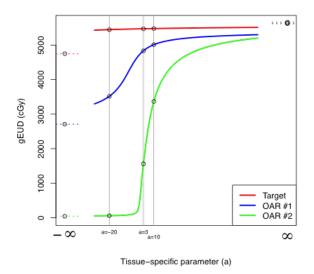
Figure 5: **Generalized equivalent uniform dose calculation for three structures.** Calculated gEUD values are shown for the PTV and two different OARs as functions of tissue-specific parameter (a) across an infinite range of values.

3.3. Three-dimensional structure analysis

Dose volume histogram data is fundamentally limited as all spatial orientation and relationships are discarded and all voxels comprising a structure are considered to be of equal dosimetric and biologic importance. No anatomically relevant location information is thus considered. Even more nuanced biological modeling (e.g. LQE or gEUD or normal tissue complication probabilities [NTCP]) is subject to the same fundamental limitation that a target or OAR are both considered to be homogeneous objects. Emerging evidence however indicates that certain key structural sub-volumes may have higher clinical significance than other sub-volumes within the same structure – a prime example of this phenomenon is the left anterior descending artery and other coronary vessels within the context of a larger cardiac OAR [15]. Novel DVH analyses are therefore increasingly predicated upon organizing dosimetric information in three-dimensional space. Evaluation tools such as a surface DVH or axially-segmented DVH can provide more detailed information to the clinician and enable novel dosimetric research. The RadOnc package is capable of standard DVH calculation from dose grid and structure set data, however it may also be used to display three-dimensional dose-volume histograms with DVH variability depicted along axial slices (Figure 6).

Assessment of relative similarities and dissimilarities among two or more structures is a common and critical aspect of three-dimensional structure analysis. This is particularly important for research comparisons among independently delineated data, and may be accomplished using the RadOnc package with metrics such as the DSC and Hausdorff distance. Generally the DSC and Hausdorff distance correlate inversely to a significant degree,
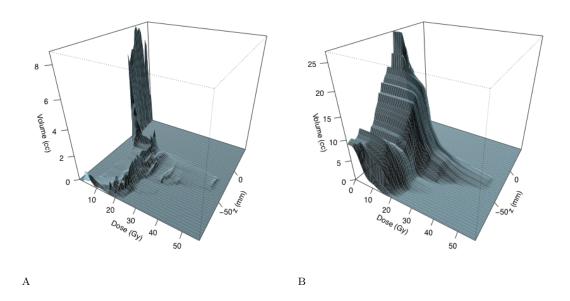
Figure 6: **Three-dimensional DVH plots for a single structure.** (A) Differential DVHs are shown for a single structure (stomach) as a three-dimensional function of dose and axial slice (z) position, equivalent to standard differential DVHs binned by axial slice. (B) Analogous data is depicted as cumulative DVH binned by axial slice.

however they are each sensitive to different perturbations. Moreover, while structural differences are summarized as single values, neither the DSC nor Hausdorff distance are able to comment on the spatial distribution of volumetric disagreement. Instead, detailed volumetric comparisons lend themselves to direct visualization as shown in Figure 7.

4. Discussion

While there are many clinical and research tools available to the radiation oncologist for individual treatment planning, plan evaluation, and focused dosimetric analysis, many hurdles remain for the integration and evaluation of such data across cohorts of patients. The RadOnc package described herein provides an extensible platform for this express purpose and has been specifically designed to facilitate clinical research.

The software herein implements multiple features that are available in other analytical software used by Radiation Oncology professionals (e.g. HART [5]). However, the implementation of the RadOnc package tools using R reduces their computational efficiency due to speed limitations in memory handling and data processing. Additionally, the RadOnc package may empower inappropriate use as it requires basic familiarity with R as well as the analytical algorithms employed. As such, the RadOnc package is not intended as a clinical workhorse, but rather as an extensible investigative tool.
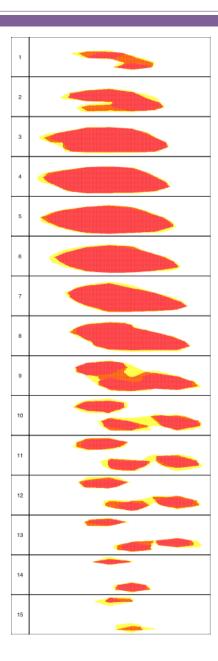
Figure 7: **Volumetric comparison of multiple independently delineated contours of a single tooth.** Each pane depicts a two-dimensional projection of a given axial slice of a tooth, displayed in descending order from cranial to caudal-most extent. The color depicts degree of overlap among independently-delineated structures, from white (external to all contours) to red (100% inclusion among all contours).

Taken together however, the RADONC package provides an interoperable and multifunctional framework that is freely available to the entire community and supported across multiple computing platforms, adding both nuance and value to the clinical researcher. The RADONC package remains under active development (R.F.T.) and supports a growing user base with regular updates and new feature implementations based upon user requests. The RADONC package is freely available on the CRAN online repository under the GNU Public License and may be adopted or adapted without restriction. The package itself is offered as open-source code and provides the opportunity for users to contribute additional functionality as desired or separately incorporate their own coding addenda.

5.   Acknowledgements

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