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Scientific Article

Statistical Analysis of Interfraction Dose Variations of High-Risk Clinical Target Volume and Organs at Risk for Cervical Cancer High-Dose-Rate Brachytherapy

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Abstract

Purpose: High-dose-rate (HDR) brachytherapy for cervical cancer treatment includes significant uncertainties. The aim of this study was to quantify the interfraction dosimetric variation (IDV) of the high-risk clinical target volume (HRCTV) from the prescribed dose and the corresponding effect on organ-at-risk (OAR) dose based on a comprehensive statistical analysis.

Methods and Materials: Fifty patients with cervical cancer treated with high-dose-rate intracavity brachytherapy from October 2019 to December 2020 were retrospectively analyzed. The OARs of interest were the rectum, bladder, sigmoid, and bowel. The dosimetric parameters evaluated for all patients was the dose absorbed by 90% of the HRCTV (D_{90}) and the dose absorbed by 0.1 ($D_{0.1cc}$) and 2 cm^3 (D_{2cc}) of each respective OAR. The HRCTV variations were from the prescribed dose and the OAR variations were from the corresponding tolerance dose. Distribution fitting of the HRCTV variations was determined to quantify the IDV. Comparative statistics of the HRCTV variations with the OAR variations were conducted to determine correlations.

Results: The mean HRCTV variation from the prescribed dose was −2.53% ± 8.74%. The HRCTV variations and OAR variations showed moderate to weak linear correlations despite the variations being relative to each other, with the bladder D_{2cc} having the strongest correlation. There was a 30.0% (±2.62%, 95% confidence interval) probability of underdosing the HRCTV (−5% variation from prescription) and a 23.3% (±2.62%, 95% confidence interval) probability of overdosing the HRCTV (+5% variation from prescription). This tendency to underdose the HRCTV was a consequence of HRCTV IDV not being normally distributed.

Conclusions: HRCTV dosimetric variations and OAR variations were complexly correlated with the bladder D_{2cc} having the strongest correlation. HRCTV IDV was best described as a left-skewed distribution that indicates a tendency of underdosing the HRCTV. The clinical significance of such dose variations is expected and will be further investigated.

Introduction

Brachytherapy procedures are subject to varying levels of uncertainties, from source construction and calibration to delivery of clinical plans.[1-3] These uncertainties can result from technology or clinical procedures.

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Uncertainties associated with clinical procedures that clinicians have control over are called clinical uncertainties. Clinical uncertainties include the uncertainties of structure delineation and organ motion.[4-14]

It is accepted that high-risk clinical target volume (HRCTV) delineation and organ-at-risk (OAR) motion are the most significant components of the brachytherapy treatment uncertainty budget.[15] At our institution, high-dose-rate (HDR) tandem and ovoid (T&O) intracavity brachytherapy (ICBT) treatments are online adaptive procedures: every fraction has a new computed tomography (CT) scan and plan, which results in interfraction dosimetric variations (IDV) of the HRCTV, especially IDVs from the prescribed dose. Although dosimetric variations may not be considered an uncertainty in statistical terms, they are considered a form of uncertainty in brachytherapy.[16] IDVs from the prescribed dose may not be dominant among HDR T&O ICBT uncertainties, but they are important as they may have a significant effect on clinical outcomes. However, this type of uncertainty has not been studied with the same rigor as the aforementioned uncertainties.

There have been studies of IDVs of OARs and the target volume or point.[12,14,17] These studies acknowledge that IDVs are forms of uncertainties in brachytherapy but mostly focus on deformable image registration (DIR) dosimetric parameters and their variation from dose-volume histogram (DVH) dosimetric parameters, not the variation of dose from the given prescription. Chakraborty et al[18] and Jamema et al[19] studied the effect of interfraction applicator position on OAR dose in cervical cancer brachytherapy in addition to the spatial change of the dosimetric parameters. However, neither focused on the IDV of the HRCTV nor its corresponding effect on OAR dose. Sharma et al studied Point A dosimetric variations from the given prescription in fractionated brachytherapy.[20] Despite the importance of continuing to use point doses in modern day cervical cancer brachytherapy, volumetric parameters such as the HRCTV have taken priority to Point A and other point dose parameters.[21]

To our knowledge, HRCTV dosimetric variations from the given prescription and the corresponding effect on OAR dose in HDR T&O ICBT have not been studied. Therefore, in this study, we evaluate the IDV of the HRCTV from the prescribed dose and the corresponding effects on OAR dose in HDR T&O ICBT. Furthermore, we studied the distribution of IDVs from the prescribed dose to quantify the corresponding uncertainty.

Methods and Materials

Data collection

Fifty patients with uterine cervix cancers and treated with HDR T&O ICBT from October 2019 to December 2020 were retrospectively analyzed. All patients were treated with prescriptions of 5 or 7 Gy per fraction for 2 to 5 fractions. There was a total of 188 fractions of HDR T&O ICBT evaluated. The delineation of structures followed the International Commission on Radiation Units report 89 (ICRU 89) and was conducted on CT images.[22] The HRCTV was delineated as the entire cervix, uterus, parametrium, and vagina. The OARs of interest were the rectum, bladder, sigmoid colon, and the bowel. Treatment planning for each fraction was conducted in the Varian Eclipse brachytherapy treatment planning system (TPS).

Statistical analysis

Dosimetric variation

The calculation of dosimetric variations was done using the percent difference equation:

$$\%\ difference = \frac{Dose\ delivered - Prescription\ or\ tolerance\ dose}{Prescription\ or\ tolerance\ dose} \times 100 \quad (1)$$

where the dose delivered is D_{90} for the HRCTV, and dose in 0.1 cc ($D_{0.1cc}$) and 2 cc (D_{2cc}) for the OARs. The tolerance dose is 80% of the prescription for the OARs. The dosimetric variations were organized by structure for each patient. The mean dosimetric variation over a patient's course of HDR T&O ICBT constituted as a data point for each structure. Thus, for each structure, there were 50 data points evaluated for the 50 patients in the study. This provided a description of each patient's IDV from the given prescription.

Basic statistics

Data analysis was performed in Python 3.7 via the use of the SciPy and DistFit packages. The mean, standard deviation, and median were calculated for each structure's dosimetric data set. From the mean and standard deviation, the coefficient of variation (CV) was determined for each structure. The CV is a measurement of consistency in the data: the higher the CV, the less consistent the data are; the lower the CV, the more consistent the data are. The 95% confidence interval (CI) was calculated for all relevant parameters.

Correlations

The Spearman correlation coefficient (ρ) was calculated for each OAR dosimetric parameter against HRCTV D_{90}. The Spearman correlation coefficient was used to determine whether a nonlinear, monotonic relationship existed between the relative variations in addition to linear relationship detection. As the correlation coefficient approaches -1 or 1, then the OAR dosimetric variation is correlated to the HRCTV dosimetric variation with a descending or ascending slope, respectively. Statistical significance for correlation coefficients was determined as $P < .05$.

Comparison of median or mean variations using Wilcoxon signed-rank test or Student t test was not necessary for this study. This is due to the values of the OAR variations from tolerance having limited clinical significance, making the comparison of median or mean OAR variations to HRCTV variation obsolete.

Data-driven distribution fitting

The HRCTV distribution was fitted to 89 different distributions using the DistFit function in Python 3.7 to find the best fit distribution. The histogram bin width can affect the fitted distribution. Therefore, distribution fitting was performed with limited dependence on histogram bin width to obtain an accurate fit.[23] To accurately fit a distribution to the HRCTV, the raw variation data was plotted as an empirical distribution, analogous to a line histogram. Each respective probability density function (PDF) was plotted along with the empirical distribution of the HRCTV. Distribution fits were ranked according to their residual sum of squares (RSS) score: the lower the score, the better the fit. The RSS is the sum of squared distances from a given point on the empirical distribution curve to the corresponding point on the PDF curve. The RSS equation is shown in Equation 2:

$$RSS = \sum_{i}^{n} (y_i - f(x_i))^2 \quad (2)$$

where n is the maximum data point, y_i is the i^{th} point of the empirical distribution, and $f(x_i)$ is the i^{th} point of the PDF. There were 50 evaluation points to fit and score the distributions.

The RSS is only a relative measurement parameter and does not determine the statistical significance of a fitted distribution. Therefore, an Anderson-Darling (AD) test was performed to determine whether the fits determined by the RSS were statistically significant.[24] The AD test uses a distribution specific term to calculate the test statistic and serves mostly as a test of normality. AD test P values >.05 or <.05 indicate that the data does or does not fit the distribution, respectively. Additionally, quantile-quantile plots of the data sets were tabulated for visual interpretations of the AD test results.

Probability of clinically significant HRCTV D_{90} variations from the given prescription calculations

Each fitted distribution has a corresponding cumulative distribution function (CDF[x]) and survival function (SF[x] = 1 − CDF[x]) as a function of dose variation of x. Evaluating CDFs at some desired value gives the probability of the variable obtaining a value less than or equal to “x.” The same can be said for calculating probabilities greater than or equal to some desired value using a distribution’s survival function, which is one minus a distribution’s CDF.

The American Brachytherapy Society (ABS) estimated an HDR dose variation of ±0.25 Gy per fraction from a given prescription.[25] This equates to a ±5% variation for 5 Gy per fraction and a ±3.57% variation for 7 Gy per fraction. This is consistent with a clinically significant dose tolerance of ±5% for radiation therapy. Where −5% variations are underdosed conditions and +5% variations are overdosed conditions. The probability of a patient’s treatment course resulting in an under- or overdose of the HRCTV was calculated using the best fitted distribution’s CDF and survival function as shown in Equations 3 and 4:

$$\textit{Under dose probability}\ (\%) = CDF(-5\%) \times 100 \quad (3)$$

$$\textit{Overdose probability}\ (\%) = (1 - CDF[5\%]) \times 100 \quad (4)$$

Robust distribution fitting

The shaping parameters that define the fitted distributions will change with additional data. Thus, the fitted distributions determined in this study from the RSS score calculations are not robust to model different data sets. To compensate for this, we also used a nonparametric approach to model the data. The data were dichotomized, where “0” was indicative of an under- or overdose incident and “1” a non−under- or overdose incident. The proportion of incidents was used to determine the probability of under- and overdosing the HRCTV as well as the probability of clinically significant variations (underdose + overdose probability). This approach provided robust estimations of the probabilities of interest without imposing any distributional assumption on the data.

Results

Basic statistics

Fifty patients and a total of 188 fractions were analyzed for D_{90} variations from the given prescription and D_{2cc} and $D_{0.1cc}$ variations from the corresponding tolerance dose. The mean variation for the HRCTV was −2.53% ± 8.74%, ranging from −25.4% to 8.90%, and the variations of up to > 20% (D_{2cc}) and > 65% ($D_{0.1cc}$) for the bladder were found, as indicated in Fig. 1. The mean and CV for all structures are tabulated in Table 1. The $D_{0.1cc}$ CV is larger than the corresponding D_{2cc} CV for all OARs except the bladder. The $D_{0.1cc}$ is accepted as a less robust parameter for dose reporting compared with the D_{2cc}.[13,21] The lower $D_{0.1cc}$ CV implies that the $D_{0.1cc}$ is more robust than the expected D_{2cc} for the bladder when evaluated as mean course variations from tolerance. Distributions of

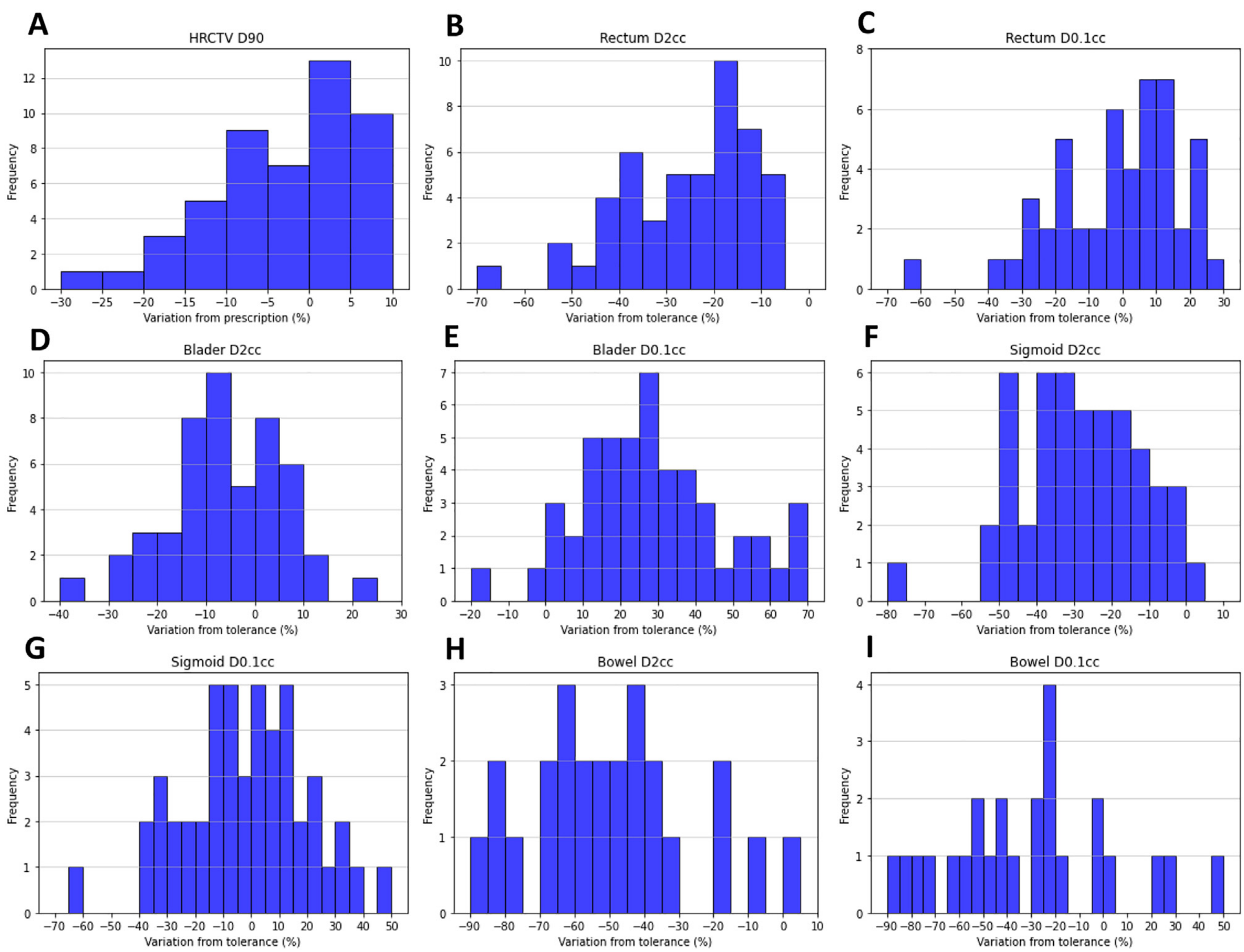

Fig. 1 Histograms of all evaluated structures (bin width = 5%). Plot A is the HRCTV D_{90} distribution, plots B and C are the rectum D_{2cc} and $D_{0.1cc}$, plots D and E are the bladder D_{2cc} and $D_{0.1cc}$, plots F and G are the sigmoid D_{2cc} and $D_{0.1cc}$, and plots H and I are the bowel D_{2cc} and $D_{0.1cc}$.

Table 1 The mean and coefficient of variation for HRCTV D_{90} and organ-at-risk $D_{0.1cc}$ and D_{2cc}

Structure and parameter	Mean ± σ variation (%)	Coefficient of variation (proportion)
HRCTV D_{90}	−2.53 ± 8.74	3.45
Rectum D_{2cc}	−25.9 ± 13.9	0.54
Rectum $D_{01.cc}$	−1.55 ± 18.7	12.1
Bladder D_{2cc}	−5.86 ± 12.0	2.05
Bladder $D_{0.1cc}$	28.4 ± 19.3	0.68
Sigmoid D_{2cc}	−28.3 ± 16.2	1.75
Sigmoid $D_{0.1cc}$	−1.73 ± 22.3	12.9
Bowel D_{2cc}	−49.8 ± 23.6	0.47
Bowel $D_{0.1cc}$	−30.6 ± 34.6	1.13

Abbreviation: HRCTV = high-risk clinical target volume.

all evaluated structures are displayed in Fig. 1. By inspection, the OAR distributions appear to take different shapes than the HRCTV distributions despite the variations being relative to each other.

Nineteen of the 50 patients had their HDR T&O ICBT course result in an average underdosing of the HRCTV with a mean variation of −11.6%. Ten of the 50 patients had their HDR T&O ICBT course result in an average overdosing of the HRCTV with a mean variation of 7.45%.

Correlations

The HRCTV D_{90} variations from the given prescription and OAR variations from the corresponding tolerance showed moderate to weak linear correlations. The rectum D_{2cc}, bladder D_{2cc} and $D_{0.1cc}$ showed statistically significant linear correlations ($r = -0.305, -0.427, -0.373$ and $P = .033, .002, .008$). Nonlinear correlations also existed for both data sets. Table 2 has the tabulated Spearman correlation coefficients (ρ) for both data sets. The nonlinear correlations showed similar statistical strength as the linear correlations. The rectum $D_{0.1cc}$ and both bowel dosimetric parameters are the only variations consistently not correlated to HRCTV variations from prescription. The rectum $D_{0.1cc}$ was only moderately uncorrelated ($\rho = -0.230$, $P = .111$), whereas both bowel dosimetric parameters were strongly uncorrelated ($P > .250$). The bladder D_{2cc} had the strongest correlation with HRCTV variations ($\rho = -0.508$, $P < .001$); the correlation is displayed in Fig. 2. The sigmoid dosimetric parameters were not correlated HRCTV variations ($P = .159$ and $P > .250$ for D_{2cc} and $D_{0.1cc}$, respectively).

Fitted distributions

HRCTV D_{90} variations from the prescription are not normally distributed (AD $P < .001$). Figure 3 displays the best fit distributions for the HRCTV D_{90} determined from the data-driven analysis (RSS scores), and the corresponding normal distributions if the variations were normally distributed. The generalized extreme value (GEV) distribution is the best fit distribution for HRCTV D_{90} (AD $P = .213$). It is important to note that the distribution of HRCTV D_{90} variations from the prescription being left skewed and nonnormal are more important than the actual fitted distribution, for the best fitted distribution may change with varying amounts of data.

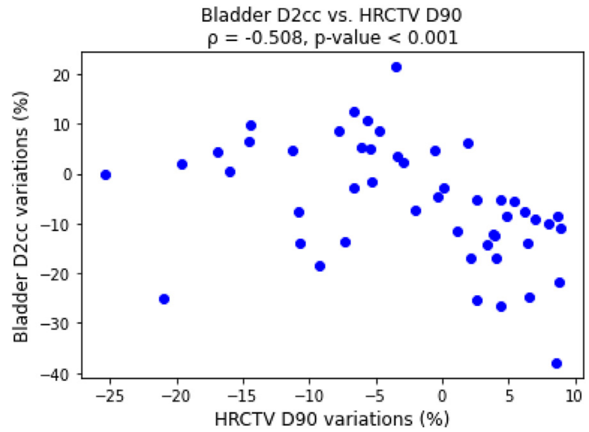

Fig. 2 Scatter plot of bladder D_{2cc} versus high-risk clinical target volume (HRCTV) D_{90}. The HRCTV D_{90} variations from prescription are on the x-axes and the corresponding bladder D_{2cc} variations from tolerance are on the y-axes.

The calculated probabilities from the GEV and normal distributions' CDF and SF of under- (−5% HRCTV D_{90} variation) and overdosing (+5% HRCTV D_{90} variation) the HRCTV, respectively, are tabulated in Table 3. The respective distributions' corresponding mean, median, and standard deviations are also tabulated in Table 3. The GEV distribution had a higher probability of underdosing the HRCTV (30.0%), compared with overdosing the HRCTV (23.3%). Figure 4 provides a visual of the HRCTV under- and overdosing probabilities calculated from the GEV's CDF.

The nonparametric distributions are displayed in Fig. 5. The underdose, overdose, and clinically significant variation probability was 38.0%, 20.0%, and 58.0%, respectively. This resulted in an 8.0% difference for underdose, 3.3% for overdose, and 4.7% for clinically significant variation compared with the GEV distribution.

Table 2 Nonlinear correlations

Structure and parameter	Spearman correlation coefficient (ρ)	P value
Rectum D_{2cc}	−0.302	.035
Rectum $D_{01.cc}$	−0.230	.111
Bladder D_{2cc}	−0.508	<.001
Bladder $D_{0.1cc}$	−0.388	.006
Sigmoid D_{2cc}	−0.204	.159
Sigmoid $D_{0.1cc}$	−0.155	>.250
Bowel D_{2cc}	0.042	>.250
Bowel $D_{0.1cc}$	0.017	>.250

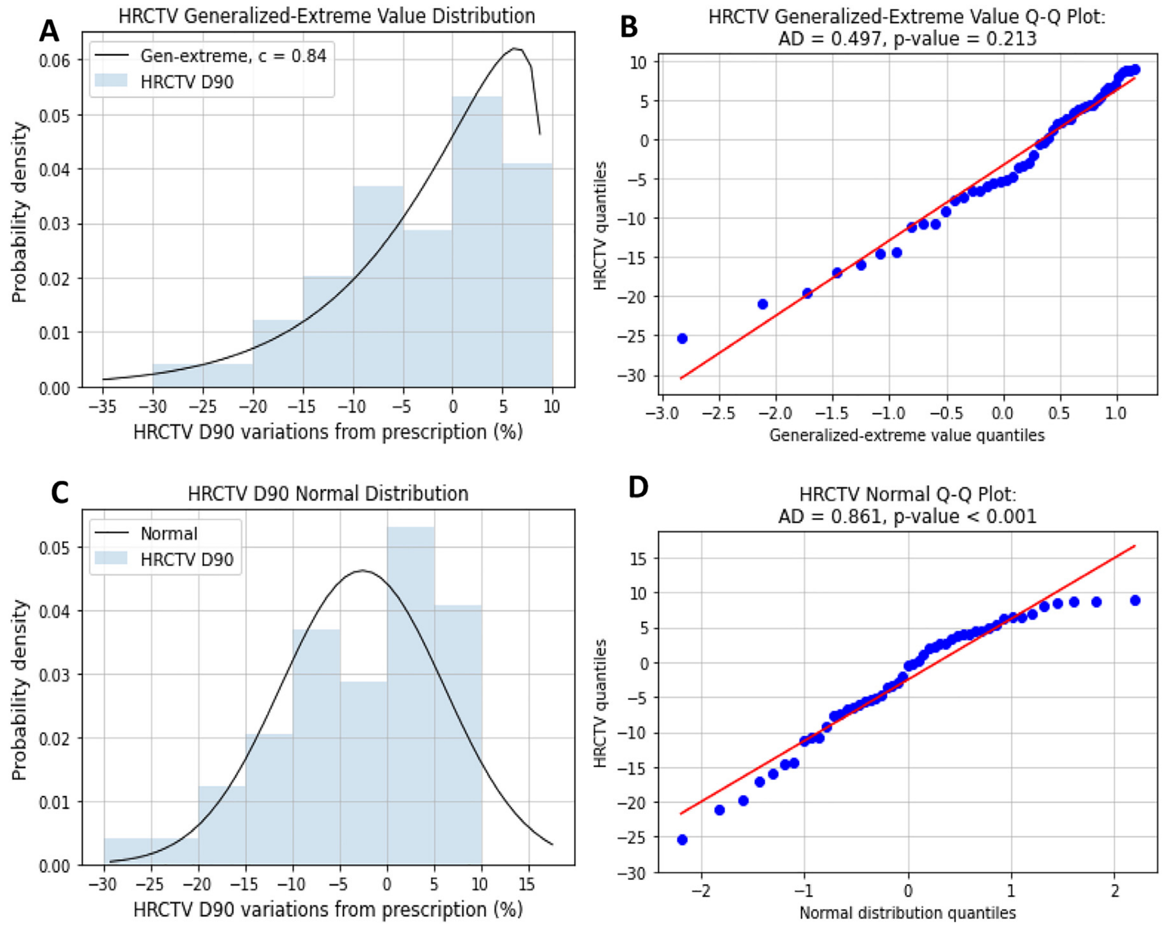

Fig. 3 Best-fitted distributions and a fitted normal distribution for high-risk clinical target volume (HRCTV) D_{90} (A, C) determined from the data-driven analysis (residual sum of squares score). The HRCTV D_{90} variations from prescriptions are on the x-axis and the corresponding probability density is on the y-axis. Quantile-quantile (Q-Q) plots and Anderson-Darling (AD) test results are also tabulated (B, D) to show the statistical strength, or lack thereof, of the fitted distributions. The respective fitted distribution quantiles are on the x-axis and the HRCTV D_{90} variations from prescription quantiles are on the y-axis. AD P values >.05 mean the distribution statistically fits the data. AD P values <.05 mean the distributions do not statistically fit the data. From the AD test and Q-Q plots, the variations are not normally distributed.

Table 4 has this study's value-relevant parameter's 95% CI tabulated. The value-relevant parameters are the mean HRCTV D_{90} variation from the given prescription, the underdose probability, and overdose probability. The clinically significant probability is implied from the underdose and overdose probabilities. The value of these parameters holds clinical significance because they give the variation from the prescribed dose and the probability of significant variations from said dose. The value of the OAR variations holds limited clinical significance because dose is not prescribed to OARs, and it is a goal to limit OAR dose as much as possible. The 95% CI is tabulated

Table 3 Probabilities and statistics from distributions*

Distribution	Underdose probability (%)	Overdose Probability (%)	Significant variation probability (%)	Mean ± SD (%)	Median (%)
Generalized extreme value	30.0	23.3	53.3	−2.32 ± 9.46	0.15
Normal	41.2	18.7	59.9	−3.00 ± 9.00	−3.00

Abbreviations: CDF = cumulative distribution function; SD = standard deviation.
*The probabilities were calculated using the generalized extreme value and normal CDF determined from their residual sum of squares scores.

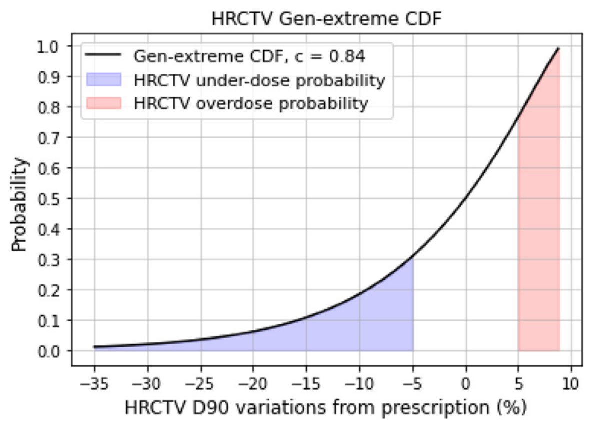

Fig. 4 Visualized probabilities of under- and overdosing the high-risk clinical target volume (HRCTV) generalized extreme value cumulative distribution function (CDF). HRCTV D_{90} variations from the given prescriptions are on the x-axis, and the probability of a corresponding variation from prescription is on the y-axis. Underdosing the HRCTV was defined as HRCTV D_{90} variations less than −5%, and overdosing the HRCTV was defined as HRCTV D_{90} variations greater than 5%.[25]

for both distribution fitting techniques: data-driven (RSS score) and nonparametric (robust).

Discussion

The variation of HRCTV dose is an important issue as it may have potential effect on clinical outcomes. However, it has not been well addressed in the literature. Sharma et al studied IDVs of the target from the prescription given at Point A and the IDV of OAR dose for point dose parameters.[20] They found that the average IDV of Point A doses from the given prescription was 1.55% ± 1.07%. In this study, HRCTV dosimetric variations from the prescription and the corresponding effect on OAR dose have been successfully evaluated., Also, large HRCTV IDVs (−2.53% ± 8.74%, from −25.4% to 8.9%) and large OAR IDVs (eg, up to >20% (D_{2cc}) and >65% ($D_{0.1cc}$) for the bladder) were obtained. Although the determination of clinical effect of IDVs should be based on clinical data and is beyond the scope of this paper, the clinical significance of the results in this study was anticipated and can be estimated based on certain models. Estimated using the dose response curves proposed by Tanderup et al,[15] up to −9.1% change in local control and 12.4% change in morbidity could be caused by the aforementioned IDVs. This estimate may not be accurate, but at least indicates such IDVs may have significant effect on clinical outcomes. More thorough and systematic analysis will be performed based on clinical data in our future studies. Complex correlations between OAR doses and

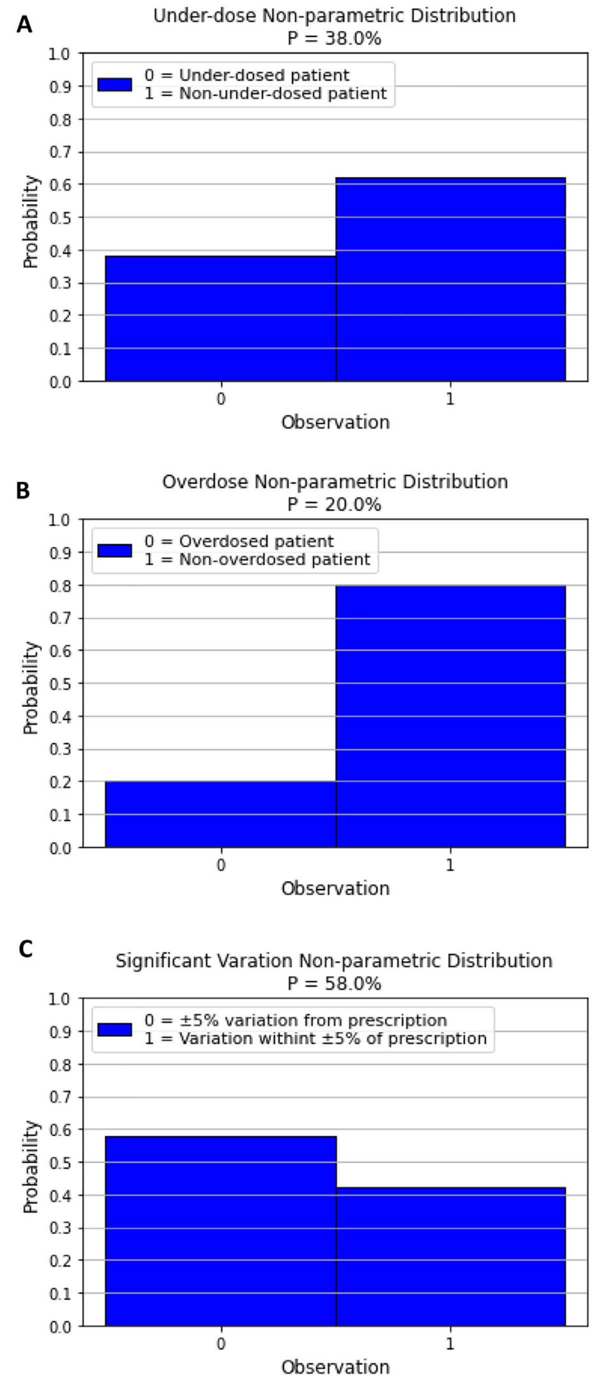

Fig. 5 Discrete non-parametric distributions for under-dosed, overdosed, and clinically significant high-risk clinical target volume D_{90} variations from the prescribed dose. On the x-axis, a value of 0 is indicative of an under- or overdose incident, while a value of 1 is indicative of a non −under- or overdose incident. On the y-axis, the probability mass function gives the probability of the observed events. Plots A, B, and C are the underdose, overdose, and clinically significant histograms.

HRCTV D90 were found in this study. A linear correlation would indicate that a simple relationship between the

Table 4 95% confidence intervals for HRCTV D_{90} variations from prescription

Data set	Variation from prescription
HRCTV D_{90} mean variation	−2.53% ± 2.42%
Data-driven underdose probability	30.0% ± 2.62%
Data-driven overdose probability	23.3% ± 2.62%
Nonparametric underdose probability	38.0% ± 2.42%
Nonparametric overdose probability	20.0% ± 2.42%

Abbreviation: HRCTV = high-risk clinical target volume.

respective variations is evident. That is, the cause of the OAR variations can simply be explained from the HRCTV variations. This is not the case. The variations show a stronger monotonic correlation than linear correlations. Monotonic functions are statistical functions with limited relevance clinically. Rather, it is stated that the relative variations are complexly correlated: there is more to the cause of the changing OAR dose than just the HRCTV dosimetric variation from prescription, despite the two being relative to each other.

Uncertainties in brachytherapy are assumed to be random and, thus, normally distributed.[16,26] Nesvacil et al studied the simulated effect of systemic and random uncertainties on tumor control probability (TCP) and normal tissue complication probability (NTCP) models.[16] Systematic uncertainties were defined as consistent errors that are out of the control of clinicians, and random uncertainties were defined as dosimetric variations. They found that TCP and NTCP models were generally robust to varying degrees of random uncertainties when combined with consistent systematic uncertainties. However, we have found that HDR T&O ICBT course dosimetric variations are not normally distributed, and, thus, cannot be assumed as a random uncertainty. The distribution of HRCTV variations is left skewed, meaning there is a higher probability of underdosing the HRCTV than overdosing the HRCTV. Assuming a normal distribution would result in either equal probabilities of under- and overdosing the HRCTV or overestimate the underdose probability and underestimate the overdose probability as we have seen from the fitted normal distribution (Table 3). Both the data-driven distribution (GEV) determined from the RSS-score (30.0% ± 2.62%, 95% CI) and robust distribution (38.0% ± 2.42%, 95% CI) support the claim that there is a tendency to underdose the HRCTV throughout a patient's course of treatment, thus meaning the distribution of variations is left skewed and nonnormal. The observed nonrandom effect of dosimetric variations on TCP and NTCP models and clinical outcomes is recommended for future studies.

The large IDVs found in this study indicated that delivering the prescribed dose to the target while sparing OARs is not always obtainable. Any techniques that can improve target coverage and OAR sparing should be encouraged to apply in clinical practice. Recently, clinical trials of hyaluronate gel injection spacers between the vagina and rectum have shown promising results in reducing rectum dose without sacrificing tumor coverage in GYN brachytherapy.[27,28] We recognize that different prescription doses and different fractionations may have different OAR dose constrains with different EQD_2 values. However, the effect of differing dose per fraction is reduced in this study because of the use of tolerance doses relative to prescription doses. The 80% tolerance is generally conservative and provides a standard and uniform analysis.[25,29,30] The clinical implications of differing dose prescriptions will be studied extensively in future research.

Interfraction contour variability and OAR motion may also affect dosimetric variations. However, interfraction contour variability and OAR motion were different uncertainties and not the focus of this study. In this study, we accepted the provided contours as the true anatomy and ignored possible OAR motion.

In this study, we only evaluated the correlations of HRCTV dosimetric variations on the $D_{0.1cc}$ and D_{2cc}. However, for larger volume organs such as the sigmoid and the bowel, the D_{5cc} and D_{10cc} via dose surface histograms (DSH) are of clinical interest and are recommended for study purposes by ICRU 89.[22] Volume coverage parameters such as the volume that receives 75% of the dose (V_{75}) for OARs and the volume that receives 100% of the dose (V_{100}) for HRCTV could also be used for evaluating HRCTV dosimetric variations from the given prescription.[22] Observations of the radiobiological effect of HRCTV dosimetric variations were not examined but will be examined in future studies. It is imperative to evaluate course variations using EQD_2 to standardize the interfraction dosimetric variations in future studies. Doing so will strengthen the analysis as cumulative EBRT and brachytherapy doses are evaluated in this manner. A proper uncertainty analysis (adding uncertainties in quadrature) of the observed variations was not conducted in this study and will be included in future studies.[2,31]

Conclusion

Dosimetric variations of the HRCTV from prescription and the corresponding effect on OAR dosimetric parameters were evaluated in this study. Complex correlations existed with HRCTV D_{90} variations from the given prescription and OAR dosimetric parameters. HRCTV D_{90} variations from the given prescription were well within the tolerance thresholds of ±5% in mean, but they formed a left-skewed distribution best described by the GEV distribution that indicated an increased probability to exceed this tolerance with an increased tendency to underdose the HRCTV. The clinical significance of such dose variations is expected and will be thoroughly and systematically investigated in future studies.

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