Postprint of a Rectal Complication Prediction Model Based on Precise Surface Dose Accumulation in Cervical Cancer Radiotherapy

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Abstract

Objective: To propose and validate a rectal complication prediction method based on accurate surface dose accumulation for cervical cancer radiotherapy. Methods: Data from 42 cervical cancer patients were retrospectively collected. The rectal wall in each treatment fraction was accurately point-registered to obtain deformation fields, which were used to deform and accumulate the dose delivered to the rectal wall, yielding a 3D total dose. The 3D rectal total dose distribution was mapped onto a 2D plane, from which dose-volume features and dose-geometric features were extracted. Features showing significant differences ($P<0.05$) in dose distribution were selected to establish a rectal complication prediction model based on sequential forward selection algorithm and logistic regression. Results: The rectal wall surface registration demonstrated high precision, with four similarity evaluation metrics indicating significant improvement in the registration degree of rectal surfaces across different treatment fractions after registration. Five-fold cross-validation results showed accuracy, sensitivity, specificity, and AUC of 79.5%, 81.3%, 75.0%, and 0.88, respectively. Conclusion: The rectal complication prediction model based on accurate surface dose accumulation proposed in this study is feasible and provides reliable support for rectal toxicity prediction in cervical cancer patients.

Full Text

Preamble

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Abstract

Objective To propose and validate a rectal complication prediction method based on accurate surface dose accumulation for cervical cancer radiotherapy. **Methods** Clinical data from 42 cervical cancer patients were retrospectively collected. The rectal wall for each treatment fraction was accurately point-registered to obtain deformation fields, which were used to deform and accumulate the rectal wall dose, yielding a 3D cumulative dose. The 3D cumulative rectal dose distribution was mapped to a 2D plane, from which dose-volume features and dose-geometric features were extracted. Features with significant differences ($P < 0.05$) were selected to establish a rectal complication prediction model based on sequential forward selection algorithm and logistic regression. **Results** The rectal wall surface registration achieved high precision, with four similarity evaluation metrics demonstrating significant improvement in registration accuracy across different treatment fractions. Five-fold cross-validation results showed accuracy, sensitivity, specificity, and AUC values of 79.5%, 81.3%, 75.0%, and 0.88, respectively. **Conclusion** The proposed rectal complication prediction model based on accurate surface dose accumulation is feasible and provides reliable support for predicting rectal toxicity in cervical cancer patients.

Keywords: cervical cancer radiotherapy; rectal complications; accurate point registration; dose accumulation; logistic regression

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Title: Rectal Toxicity Prediction Based on Accurate Rectal Surface Dose Summation for Cervical Cancer Radiotherapy

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Abstract: Objective To propose a rectal toxicity prediction method based on deformable surface dose accumulation. Methods The clinical data were collected retrospectively from 42 patients receiving radiotherapy for cervical cancer. With the first fraction as the reference, the other fractions of rectum surface were registered to the reference fraction to obtain the deformation vector fields (DVFs), which were used to deform and sum the fractional rectal doses to yield the cumulative rectal dose. The cumulative rectal dose was flattened via 3D-2D mapping to generate a 2D rectum surface dose map. Two dosimetric features, namely DVPs and DGPs were extracted. Logistic regression embedded with sequential forward feature selection was used as the prediction model. The predictive performance was evaluated in terms of the accuracy, sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve (AUC). Results Significant improvements for rectum surface DIR were achieved. The best predictive results were achieved by using both DVPs and DGPs as the features with a sensitivity of 79.5%, a specificity of 81.3% and an AUC of 0.88. Conclusion The proposed method is feasible for predicting clinical rectal toxicity in

patients undergoing radiotherapy for cervical cancer.

Keywords: cervical cancer; rectum toxicity; deformable registration; dose accumulation; logistic regression

Introduction

The primary radiotherapy regimen for locally advanced cervical cancer [1] consists of external beam radiotherapy (EBRT) and brachytherapy (BT). Increasing the radiation dose to the target volume is an effective means to improve local control rates for cervical cancer [2]. However, high-dose irradiation inevitably increases radiation toxicity to organs at risk (OARs), such as the rectum, sigmoid colon, bladder, and vagina, thereby elevating the risk of radiotherapy complications [3-4].

Currently, the clinical evaluation of OAR radiation toxicity primarily follows the dose-volume parameters D0.1cc, D1cc, and D2cc recommended in the ICRU Report 89 [5] (minimum point dose within the highest irradiated volume of 0.1, 1, and 2 cm^3, respectively). D0.1/1/2cc is based on a worst-case scenario assumption that completely disregards organ deformation, assuming that high-dose points in OARs remain static across different radiotherapy fractions [6-7]. However, interfractional variations inevitably exist, including patient setup errors and OAR displacement and deformation, causing the D0.1/1/2cc values in the radiotherapy plan to be higher than the actual delivered dose. While this assumption protects OARs by overestimating the delivered dose, it simultaneously constrains dose escalation to the target volume. Current studies have used grayscale-based image registration algorithms to achieve interfractional dose accumulation and obtain the true cumulative delivered dose. However, the resulting dose-volume parameters show no significant differences from those based on the worst-case assumption, failing to yield truly accurate dose distributions [8-10]. Furthermore, dose-volume parameters D0.1/1/2cc represent one-dimensional point doses that do not contain spatial geometric distribution information of the dose. Numerous studies have demonstrated [11-14] that localized dose distribution information in the rectum is closely correlated with rectal toxicity. Nevertheless, these statistical analysis-based methods cannot directly predict the probability of OAR complications. Inspired by the recent rise of machine learning, we have incorporated spatial dose distribution information to establish a prediction model for evaluating radiation toxicity, aiming to fully understand the relationship between radiation dose distribution and OAR toxicity.

This study innovatively proposes a rectal complication prediction method for cervical cancer radiotherapy based on accurate surface dose accumulation to predict the relationship between rectal delivered dose and rectal radiation toxicity, enabling sufficient dose escalation to the target while reducing OAR dose.

1.1 Study Subjects

This study retrospectively collected clinical data from 42 cervical cancer radiotherapy patients, including planning CT images and treatment plans. All patients received external beam radiotherapy (EBRT) and brachytherapy (BT), with EBRT doses of 50 Gy/25 fractions at 2 Gy per fraction, and BT doses of either 28 Gy/4 fractions at 7 Gy per fraction or 30 Gy/5 fractions at 6 Gy per fraction. Patients underwent follow-up examinations every 2-3 months after treatment, with those experiencing hematochezia symptoms receiving further colonoscopy. Based on rectal toxicity grading scores, the 42 patients were divided into two categories: those with rectal complications post-radiotherapy (Grade 2 rectal toxicity, 12 cases) and those without complications (Grade 0-1, 30 cases).

1.2 Methods Overview

Clinicians manually delineated the rectal outer contour to obtain rectal mask images. Using a particle-based anisotropic surface mesh generation method [15], the rectal contours from each treatment fraction were converted into uniform rectal surface mesh points. The rectal wall surface mesh points from the first treatment fraction served as the reference point set, and an accurate point registration algorithm (TOP-DIR) [16] proposed by our team was used to register the rectal wall across all fractions. The calculated deformation fields were employed to deform and accumulate the fractional rectal wall doses, yielding the total cumulative dose, which was then converted to 2 Gy equivalent dose (EQD2) [17-19]. Through 3D-2D transformation, the 3D cumulative rectal dose distribution was mapped onto a 2D plane. Dose-volume features (DVPs) and dose-geometric features (DGPs) were extracted from both the 3D dose distribution and the mapped 2D dose distribution, and features with significant differences ($P < 0.05$) were selected. A sequential forward selection algorithm [20] was used for feature selection, and a logistic regression algorithm was employed to establish a rectal complication prediction model (LR-SFS). Five-fold cross-validation was used to evaluate the model' s predictive performance. Additionally, the predictive capability of DVPs and DGPs was compared against traditional dose-volume parameters D0.1cc, D1cc, and D2cc (WS-D0.1/1/2cc) based on the worst-case scenario assumption.

1.2.1 TOP-DIR Rectal Surface Point Registration

TOP-DIR is a non-rigid point registration method based on the TPS-RPM algorithm [21]. It defines a 3D floating point set V = {v_i = (v_xi, v_yi, v_zi) | i = 1,2,⋯,K} and a reference point set X = {x_j = (x_xj, x_yj, x_zj) | j = 1,2,⋯,N}. The TPS-RPM algorithm iteratively solves for the correspondence matrix M and mapping function f by minimizing the following energy function:

$$E(M,f) = \sum_{i=1}^{K+1}\sum_{j=1}^{N+1} m_{ij}\|x_j - f(v_i)\|^2 + \lambda\|Lf\|^2 + T\sum_{i=1}^{K+1}\sum_{j=1}^{N+1} m_{ij}\log m_{ij}$$

where L is the thin-plate spline smoothing regularization operator and M is the fuzzy correspondence matrix between the floating and reference point sets. The TOP-DIR algorithm enhances this by replacing the original correspondence matrix m_ij with a new matrix P_ij that incorporates neighborhood information constraints during the iterative update step:

$$P_{ij} = \frac{m_{ij}S_{ij}}{\sum_{k=1}^{N} m_{ik}S_{ik}}$$

where S_ij represents the neighborhood similarity constraint:

$$S_{ij} = \sum_{s\in\mathcal{N}(v_i)}\sum_{t\in\mathcal{N}(x_j)} R_{ij}(s,t)m_{st}$$

$$R_{ij}(s,t) = \alpha_{ijst}\cdot\beta_{ijst}$$

$$\alpha_{ijst} = 1 - \frac{|d(v_i,v_s) - d(x_j,x_t)|}{\max(d(v_i,v_m), d(x_j,x_n))}$$

$$\beta_{ijst} = \frac{1}{d(v_i,v_s)}\cdot\frac{1}{d(x_j,x_t)}$$

where d denotes the Euclidean distance between two points. represents the similarity between the distance of neighboring point pair (v_i, v_s) and that of (x_j, x_t), with larger indicating greater similarity. represents the distance weighting of point v_i to its neighbor v_s and point x_j to its neighbor x_t, with larger when v_s is closer to v_i and x_t is closer to x_j.

1.2.2 Dose Accumulation and 3D-2D Dose Mapping

After point registration, deformation fields for each point on the rectal surface were obtained. B-spline interpolation [22] was used to compute the deformation field for the entire 3D dose distribution, which was then used to deform and accumulate the 3D dose across all fractions, yielding the total cumulative 3D dose to the rectal wall. The process of mapping the 3D cumulative rectal dose distribution onto a 2D plane was as follows: For each slice of the rectal wall contour, the geometric center was calculated. From this center, n (n = 30) equally spaced rays (12° intervals) were cast, intersecting the rectal wall at n points, and the corresponding dose values were recorded. Considering the

hollow structure of the rectum, the dose values from each slice were unfolded, transforming the 3D dose distribution into a z × n 2D dose matrix, where z is the physical length of the rectum and n is the number of sampling points. The unfolding began at the posterior side of the rectum (Figure 1 [Figure 1: see original paper]).

1.2.3 Dose Feature Extraction

Two types of dose features, DVPs and DGPs, were extracted from both the 3D dose distribution and the mapped 2D dose distribution. DVPs were defined as dose-volume features D_x-cc, representing the minimum point dose within the highest irradiated volume of x cm^3, where x [0.1, 10] at 0.5 cm^3 intervals, yielding 21 dose-volume features. DGPs were defined as geometric features extracted from dose regions at different dose levels (45 Gy to 100 Gy, at 1 Gy intervals), including relative area, perimeter, relative transverse width, and longitudinal height, totaling 224 dose-geometric features.

1.2.4 Rectal Complication Prediction Model

This study employed the sequential forward selection algorithm for feature parameter screening in logistic regression. The purpose of feature selection is to identify the optimal feature subset, eliminate irrelevant or redundant features, reduce feature dimensionality, and improve model accuracy. Given a feature set F = (f1, f2, ···, fn) and a model objective function J(•), feature selection aims to identify a subset S from F such that J(S) > J(T) for any other subset T. In the sequential forward selection algorithm, the feature subset X starts from an empty set. Through five-fold cross-validation, the first feature that optimizes the objective function J is selected from all features. Subsequently, one feature x is added at a time from the remaining unselected features to X to optimize J. This process repeats until J reaches its optimal value.

The logistic regression classifier is expressed as:

$$h_\theta(x) = \frac{1}{1 + e^{-\theta^T x}}$$

where h_ (x) is the predicted value, x = (x1, x2, ···, xn)^T is the feature vector in the model, = (0, 1, 2, ···, n) are the feature weight parameters, and n is the number of features.

Since the model parameters are computed using maximum likelihood estimation, the conditional probability P(y|x) = h_ (x)^y (1 - h_ (x))^{1-y} yields the likelihood function:

$$L(\theta) = \prod_{i=1}^{m} h_\theta(x_i)^{y_i}(1 - h_\theta(x_i))^{1-y_i}$$

where m is the number of data samples.

1.2.5 Statistical Analysis

The Mann-Whitney U test (two independent samples rank-sum test) was used to analyze statistical differences in DVPs and DGPs between the complication experimental group and the non-complication control group. $P < 0.05$ indicated statistically significant differences between the two groups.

2.1 Rectal Surface Point Registration

Rectal wall registration results are shown in Figure 2 [Figure 2: see original paper]. TOP-DIR achieved satisfactory registration results for cases with small deformation, large deformation, and complex deformation, demonstrating good robustness. Quantitative metrics for evaluating registration accuracy included Dice' s coefficient (DC), percent error (PE), mean vertex-to-vertex distance (VVD), and Hausdorff distance (HD). Higher DC values indicate better accuracy, while lower PE, VVD, and HD values indicate better accuracy. As shown in Table 1 , rectal wall surface registration achieved high precision, with DC improving from 0.71 to 0.86 ($P < 0.001$), and PE, VVD, and HD decreasing from 0.62, 1.51 mm, and 7.02 mm to 0.26 ($P < 0.001$), 0.74 mm ($P < 0.001$), and 3.97 mm ($P < 0.001$), respectively.

2.2 Quantitative Analysis of Prediction Models

After statistical analysis of DVPs and DGPs, dose distribution features with significant differences ($P < 0.05$) were selected, including 13 DVPs and 19 DGPs. A model based on sequential forward feature selection and logistic regression was then used to predict rectal radiation toxicity, with predictive performance evaluated through five-fold cross-validation. Accuracy metrics included sensitivity (SEN), specificity (SPE), accuracy (ACC), and area under the ROC curve (AUC), where SEN = TP/(TP+FN), SPE = TN/(TN+FP), and ACC = (TP+TN)/(TP+FP+FN+TN), with TP representing true positives, TN true negatives, FP false positives, and FN false negatives. Experimental results are shown in Table 2. Traditional WS-D0.1/1/2cc achieved prediction sensitivity, specificity, accuracy, and AUC of 68.3%, 67.6%, 68.0%, and 0.74, respectively. DVPs showed substantially improved predictive capability compared to WS-D0.1/1/2cc, indicating that dose-volume features beyond D0.1/1/2cc also correlate with rectal toxicity. Furthermore, after incorporating DGPs with spatial dose information, the DVPs+DGPs combination achieved optimal predictive performance with sensitivity, specificity, accuracy, and AUC of 81.3%, 75.0%, 79.5%, and 0.88, respectively. Figure 3 [Figure 3: see original paper] shows the ROC curve comparison for LR-SFS models built with different feature combinations, demonstrating that DVPs+DGPs yields the optimal ROC curve.

Discussion

Currently, clinical practice follows the dose-volume parameters D0.1cc, D1cc, and D2cc recommended in the ICRU Report 89 [8] to evaluate OAR radiation

toxicity. However, the evaluation and prediction of rectal toxicity remain active research topics in cervical cancer radiotherapy. Studies have shown [23,24] that D5cc is more reliable than other dose-volume parameters for predicting rectal mucosal lesions and late rectal complication risks. Similar to these reported studies, our experimental results demonstrate that the rectal toxicity prediction model constructed using DVPs achieves higher predictive accuracy than that based on WS-D0.1/1/2cc, reflecting that dose parameters beyond conventional D0.1cc, D1cc, and D2cc also correlate with OAR radiation toxicity.

Since D0.1/1/2cc is calculated without considering organ deformation—assuming that high-dose points in OARs remain static across different radiotherapy fractions [13-14]—and given that OARs such as the rectum and bladder often undergo substantial interfractional deformation, the estimated D0.1/1/2cc values frequently fail to reflect the true delivered dose. Therefore, an accurate and effective deformable registration algorithm is needed for precise rectal surface registration to achieve accurate dose accumulation. Among current image registration algorithms, intensity-based methods are unsuitable for rectal registration due to low contrast between the rectum and surrounding tissues, particularly in CT images. Without tissue contours or fiducial markers, intensity-based algorithms cannot handle large rectal deformations, as confirmed by related studies [25-26]. Conversely, structure-based or feature-point-based deformable registration algorithms [27-33] achieve higher registration accuracy for organs with large deformation or weak contrast. The TOP-DIR algorithm [16] proposed by our research group, based on TPS-RPM [21] and capable of preserving local topology, is more suitable for highly deformable hollow organs such as the bladder and rectum. It addresses interfractional rectal deformation, enables precise acquisition of rectal surface dose distribution, and more accurately reflects the dose-toxicity relationship, providing the possibility for further target dose escalation.

Furthermore, since D0.1/1/2cc represents one-dimensional point doses without spatial geometric distribution information, reported studies have demonstrated significant correlations between spatial dose distribution information and toxicity. For example, Drean et al. [34] found that rectal bleeding risk is primarily associated with the region between the anterior rectum and upper anal canal, while Munbodh et al. [35] reported significant relationships between late rectal toxicity and dose to the upper rectal region. Due to the hollow structure of the rectum, projecting the 3D dose distribution onto a 2D plane facilitates extraction of dose-geometric features from the 2D distribution while preserving spatial dose information, providing additional benefits for building rectal complication prediction models. Our experimental results demonstrate that incorporating DGPs yields higher predictive accuracy than using DVPs alone, corroborating the correlation between spatial dose distribution information and toxicity.

In cervical cancer radiotherapy, surrounding normal tissues and OARs inevitably sustain radiation damage, with the probability of radiation complications closely related to both the magnitude and distribution of delivered dose. Simple statistical analysis methods using dose-volume parameters D0.1cc,

D1cc, and D2cc cannot directly reflect toxicity probability. With the rapid rise of machine learning, increasing numbers of researchers [36-39] have applied it to predict normal tissue complication probability or local tumor control probability in radiotherapy. For example, Chen et al. [36] used a support vector machine model to predict radiation-induced pneumonitis in non-small cell lung cancer radiotherapy, achieving favorable predictive accuracy (AUC = 0.76). However, these studies utilized only one-dimensional dose-volume parameters or patient information as features, without incorporating spatial dose distribution information. In this study, we propose applying machine learning algorithms to predict rectal toxicity in cervical cancer radiotherapy, incorporating not only one-dimensional dose-volume parameters but also spatial geometric distribution information of rectal dose as feature parameters. Experimental results demonstrate that this approach effectively improves model predictive performance.

Although rectal dose is the most direct cause of radiation proctitis, numerous factors such as patient gender, age, and rectal radiation tolerance may also correlate with the occurrence and severity of radiation proctitis. This study focused primarily on clinical dosimetric parameters without considering these clinical factors, which will be included in future work for further validation. Additionally, due to the small sample size of collected cervical cancer patient data and the large number of extracted features relative to the sample size, we employed statistical analysis to screen for significant features and used sequential forward feature selection for dimensionality reduction to minimize overfitting risk. Cross-validation was applied to ensure model robustness. Although current results are based on cross-validation analysis, the findings demonstrate the feasibility of the proposed rectal toxicity prediction model, providing a new direction for future research on the relationship between rectal delivered dose and radiation toxicity.

Conclusion

This study obtained accurate cumulative rectal surface dose through TOP-DIR point registration, extracted 3D and 2D dose distribution features from the rectal surface dose distribution, and established a rectal radiation toxicity prediction model. Experimental results demonstrate that the proposed prediction model based on accurate surface dose accumulation can predict rectal radiation toxicity in cervical cancer radiotherapy with good accuracy, assisting radiation oncologists in designing better treatment plans. This approach holds promise for more effective and safe target dose escalation, thereby improving local control rates for locally advanced cervical cancer.

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Figure Captions

Figure 1 Schematic diagram of 3D-2D dose mapping. Illustration of unfolding the 3D rectum surface dose (left) to a 2D rectum surface dose map (right).

Figure 2 TOP-DIR registration results for three cases: small deformation (left), large deformation (middle), and complex deformation (right). Three examples of rectum TOP-DIR with small, large and complex deformation.

Figure 3 ROC curve comparison of LR-SFS models built with different feature combinations. ROC analysis for different feature combinations via LR-SFS.

Table Captions

Table 1 Comparison of DC, PE, VVD, and HD before and after rectum surface registration by TOP-DIR (Mean±SD)

Table 2 Comparison of prediction accuracy for different feature combinations

Note: Figure translations are in progress. See original paper for figures.