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Enhanced prediction of postoperative radiotherapy-induced esophagitis in non-small cell lung cancer: Dosiomic model development in a real-world cohort and validation in the PORT-C randomized controlled trial

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Abstract

Background: Radiotherapy-induced esophagitis (RE) diminishes the quality of life and interrupts treatment in patients with non-small cell lung cancer (NSCLC) undergoing postoperative radiotherapy. Dosimetric models showed limited capability in predicting RE. We aimed to develop dosiomic models to predict RE.

Methods: Models were trained with a real-world cohort and validated with PORT-C randomized controlled trial cohort. Patients with NSCLC undergoing resection followed by postoperative radiotherapy between 2004 and 2015 were enrolled. The endpoint was grade ≥2 RE. Esophageal three-dimensional dose distribution features were extracted using handcrafted and convolutional neural network (CNN) methods, screened using an entropy-based method, and selected using minimum redundancy and maximum relevance. Prediction models were built using logistic regression. The areas under the receiver operating characteristic curve (AUC) and precision-recall curve were used to evaluate prediction model performance. A dosimetric model was built for comparison.

Results: A total of 190 and 103 patients were enrolled in the training and validation sets, respectively. Using handcrafted and CNN methods, 107 and 4096 features were derived, respectively. Three handcrafted, four CNN-extracted and three dosimetric features were selected. AUCs of training and validation sets were 0.737 and 0.655 for the dosimetric features, 0.730 and 0.724 for handcrafted features, and 0.812 and 0.785 for CNN-extracted features, respectively. Precision-recall curves revealed that CNN-extracted features outperformed dosimetric and handcrafted features.

Conclusions: Prediction models may identify patients at high risk of developing RE. Dosiomic models outperformed the dosimetric-feature model in predicting RE. CNN-extracted features were more predictive but less interpretable than handcrafted features.

KEYWORDS
convolution neural network, dosiomics, non-small cell lung cancer, prediction model, radiation esophagitis

Zeliang Ma and Bin Liang contributed equally to the study.

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INTRODUCTION

For patients with non-small cell lung cancer (NSCLC), postoperative radiotherapy (PORT) reduces the risk of locoregional recurrence[1,2] and is recommended by NCCN guidelines for selected patients with high-risk N2 disease. However, PORT may have toxic side effects, including radiotherapy-induced esophagitis (RE). RE symptoms include retrosternal or substernal burning, pain, odynophagia, dysphagia, anorexia, and weight loss. RE has been reported to occur in 39% of patients undergoing PORT,[2] diminishing quality of life and potentially involving treatment interruption, which could reduce overall survival.[3]

Several dosimetric factors were identified as predictors of RE, including mean esophageal dose (Dmean)[4] and volume of the esophagus (Vx) receiving greater than 35 Gy (V35),[5,6] 40 Gy (V40),[7] 50 Gy (V50),[7,8] and 60 Gy (V60). Dosimetric factors contain only partial dose distribution information.[9,10] For example, Vx is a discrete dose–volume histogram (DVH) point, limiting predictive ability and reproducibility. Moreover, DVH collapses the three-dimensional (3D) dose distribution into one dimension, thereby failing to consider spatial distribution information.

Inspired by radiomics, dosiomics was proposed to parameterize the dose distribution of regions of interest using textural features, allowing the dose distribution to be described in the spatial dimension. Dosiomic features can be extracted using a handcrafted method containing a large panel of engineered features. Handcrafted features have been used to predict radiation esophagitis,[11,12] pneumonia,[13] xerostomia,[14] hypothyroidism,[15] and genitourinary toxicity.[16] Handcrafted features contain, but do not fully reflect, 3D dose distribution information. If well-trained, the convolutional neural network (CNN) method reveals subtle features hidden in the original data. Theoretically, a CNN may be more valuable than omics for feature extraction. Several studies have validated the feasibility of using CNN-extracted features for radiotherapy toxicity prediction, including xerostomia in head and neck carcinoma radiotherapy,[17] hepatobiliary toxicity in liver cancer radiotherapy,[18] and rectal toxicity in cervical cancer radiotherapy.[19]

To our knowledge, no previous study has used CNN-extracted dosiomic features to predict RE. Thus, we used handcrafted and CNN methods to extract dosiomic features in RE prediction and compared both with a dosimetric feature-based model.

METHODS

Patients and treatments

A real-world cohort was used for training and validation (hyperparameter tuning) models. A prospective cohort from PORT-C randomized controlled trial[1] was used as the validation set. Patients with histologically confirmed pIIIA-N2 NSCLC, according to the American Joint Committee on Cancer staging system, seventh edition, who underwent resection followed by PORT between 2004 and 2015, were enrolled. Patients were excluded if they had undergone pneumonectomy, had a history of other cancers, or received neoadjuvant chemotherapy. Clinical target volume included the ipsilateral hilum, subcarinal region, ipsilateral mediastinum, and stump of the central lesion. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Institutional Review Board of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. The requirement for informed consent was waived owing to the retrospective nature of the research.

A total dose of 50 Gy was delivered in 25 fractions at 2 Gy per fraction, 5 days per week. The radiation dose constraint for the esophagus was V50 < 50%. The endpoint was symptomatic (grade ≥2) RE according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Grade 1 RE does not affect the patient's quality of life due to the absence of symptoms; thus, grade 1 was merged with no RE.

All patients received intensity-modulated radiotherapy or 3D conformal radiotherapy. CT image slices of 5 mm thickness with the patient in the supine position were obtained using a Brilliance Big bore scanner (Philips Healthcare) and iodine-based intravenous contrast. Treatment plans were designed using a Pinnacle treatment planning system (version 9.0, Philips). The dose calculation algorithm was an adaptive convolution, and the grid size (spatial resolution of the dose distribution) was $0.4 \times 0.4 \times 0.4$ cm.

Feature extraction

The esophagus, including the wall and cavity, was delineated by experienced radiotherapists. Dosiomic features were extracted from the 3D dose distribution within the esophagus using handcrafted features and CNN methods.

Handcrafted features method

The handcrafted features method directly calculates a set of indices that describe the shape of the esophagus, first-order statistics, and texture features of the dose distribution. The following 107 handcrafted features were derived from the dose distribution: shape (14 features), first-order (18 features), gray-level co-occurrence matrix (GLCM) (24 features), gray-level dependence matrix (14 features), gray-level size zone matrix (16 features), gray-level run length matrix (16 features), and neighboring gray-tone difference matrix (5 features). The definitions and explanations have been previously described.[20]

CNN method

Convolutional layers of a pretrained 3D convolution network were used as a feature extractor containing five cascading layers and one or two convolution blocks followed by a max-pooling layer. All kernels had dimensions of $3 \times 3 \times 3$. The convolution and max pooling stride steps were one and two voxels. The network was trained using the UCF101 video dataset and was designed for video recognition.[21] Trained network details are presented in Figure S1.

A total of 4096 features were extracted using CNN. The feasibility of using CNN for 3D dose distribution-based RP prediction has been demonstrated.[22] A transfer learning strategy was used because the number of patients was insufficient for training a CNN from scratch.

Feature selection

Feature selection was performed separately for each set of features, including DVH-based, handcrafted, and CNN-based features. We used an entropy-based method for feature filtering and the minimum redundancy maximum relevance (mRMR) method for feature selection.[20] Based on previous studies, V20, V60, equivalent uniform dose (EUD), and the maximum dose (Dmax) were selected as predictors.[9,23,24] Singular outliers were removed using an unsupervised entropy-based filtering method to improve the generality and stability of the prediction model. The mRMR[25] method was then used to rank all extracted features based on their relevance to RE, and redundant features were excluded. We used the mRMR method to assess subsets of randomly selected samples (80% of the total population) and repeated random sampling and mRMR 100 times using the bootstrap method. Features with high selected times were finally selected to train models. All features were scaled using z-score normalization. Details regarding the entropy-based and mRMR methods can be found in the Supporting Information.

Model training

Prediction models were constructed using logistic regression. Five-fold cross-validation was adopted in the training process, and a nested sampling method was adopted for hyperparameter tuning. Details of the nested sampling method are shown in Figure S2. An "inner" four-fold cross-validation was nested in an "outer" five-fold cross-validation. Nested sampling split the training dataset into hyperparameter tuning (80%) and validation (20%) subsets. Hyperparameter-tuning was conducted on the inner cross-validation subset, and the model with the best performance was selected. Nested sampling was repeated 100 times using the bootstrap method. The selected features were tuned and validated using training and validation sets.

Statistics and model evaluation

Continuous variables are shown as mean ± standard deviation for normal distributions and median ± interquartile range for non-normal distributions. Categorical variables are shown as counts and percentages. Continuous variables were compared using *t*-tests or Wilcoxon rank-sum tests; categorical variables were compared using χ^2 tests or Fisher's exact tests. *p*-values <0.05 were regarded as statistically significant. The prediction models were evaluated using the area under the receiver operating characteristic curve (AUC) and precision-recall curve methods. Details regarding the calculation of these indices can be found in the Supporting Information.

Data preprocessing was performed using MATLAB software (MathWorks). Handcrafted features were extracted using the Python Pyradiomics package (version 2.0.0). CNN was constructed and trained using the TensorFlow library in Python (version 1.4.0). mRMR was implemented using the R mRMRe package (version 2.1.1). Model training was implemented using the R mlr package (version 2.19.0).[26]

RESULTS

Patient characteristics

A total of 293 patients were eligible for the study. Among them, 33 (11.26%) developed grade 2 RE, and none developed grade ≥3 RE. The mean dose to the esophagus was 27.61 ± 9.29 Gy, and the mean V50 value was 33.39% ± 19.62%. The detailed dosimetric parameters of the esophagus can be found in Table S1. Clinical characteristics were recorded according to clinical practice (Table 1). A total of 190 and 103 patients were enrolled in the training and validation set.

Model evaluation

The model was assessed using validation datasets ($N = 103$). The average AUC of the logistic regression model with handcrafted features and CNN-extracted features was demonstrated (Figure 1). As the number of selected features increased, the AUC tended to increase and then decrease. AUC values were 0.737 and 0.655 for the dosimetric feature-based model, 0.730 and 0.724 for handcrafted features, and 0.812 and 0.785 for CNN-extracted features in training and validation sets, respectively (Figure 2). Precision-recall curves also showed that CNN-extracted features outperformed dosimetric and handcrafted features (Figure 3).

The highest AUC was achieved using three handcrafted and four CNN-extracted features. Selected handcrafted features were glcm_sum of squares, glcm_correlation, and shape_flatness (Table S2). Definitions and explanations of these features can be found in the Supporting Information. Three CNN-extracted features were selected; however,

TABLE 1 Patient characteristics.

		Overall	Training set	Test set	*p*-value
n		293	190	103	
Sex (%)	Male	179 (61.09)	121 (63.68)	58 (56.31)	0.27
	Female	114 (38.91)	69 (36.32)	45 (43.69)	
Age (median [IQR])		56.00 [49.00, 61.00]	56.00 [49.00, 61.00]	56.00 [51.00, 61.50]	0.44
Smoking history (%)	Absence	138 (47.10)	85 (44.74)	53 (51.46)	0.33
	Presence	155 (52.90)	105 (55.26)	50 (48.54)	
T stage (%)	1	66 (22.53)	40 (21.05)	26 (25.24)	0.31
	2	183 (62.46)	118 (62.11)	65 (63.11)	
	3	39 (13.31)	27 (14.21)	12 (11.65)	
	4	5 (1.71)	5 (2.63)	0 (0.00)	
Tumor location (%)	Left Lung	123 (41.98)	82 (43.16)	41 (39.81)	0.67
	Right Lung	170 (58.02)	108 (56.84)	62 (60.19)	
Histology (%)	SCC	71 (24.23)	52 (27.37)	19 (18.45)	0.12
	Non-SCC	222 (75.77)	138 (72.63)	84 (81.55)	
Radiation esophagitis (%)	Grade 1 or no RE	260 (88.74)	168 (88.42)	92 (89.32)	0.97
	Grade 2	33 (11.26)	22 (11.58)	11 (10.68)	
	Grade 3–5	0	0	0	

Abbreviations: IQR, interquartile range; RE, radiation esophagitis; SCC, squamous cell carcinoma.

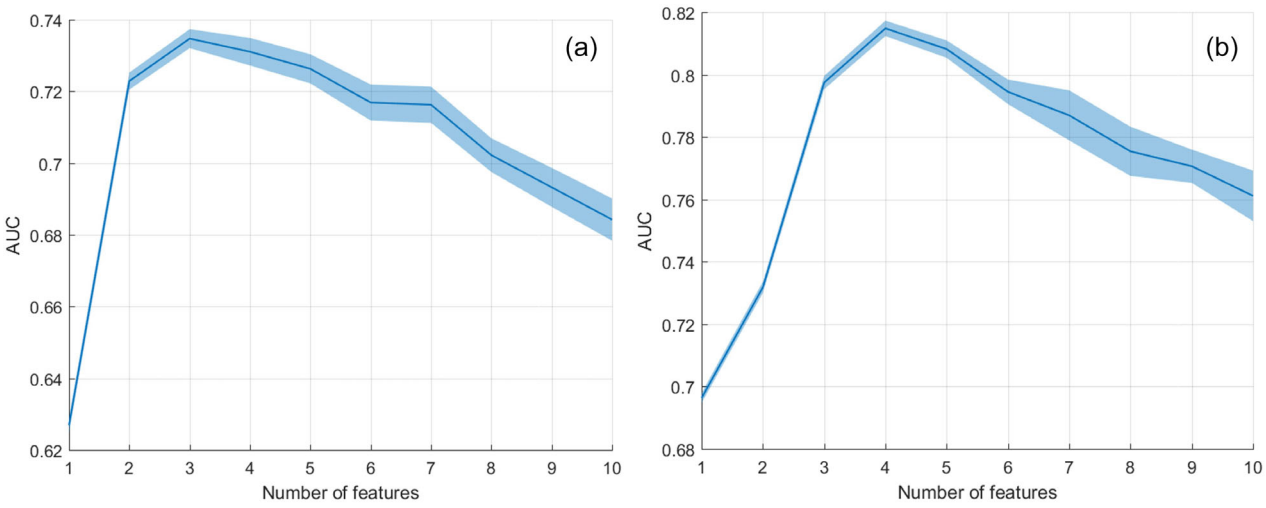

FIGURE 1 AUC and Fn feature values. AUC as a function of Fn values of handcrafted (a) and CNN-extracted (b) features are shown. For each specific Fn, the logistic regression model was hyperparameter-tuned, and the mean AUC of 100 bootstraps was calculated, along with the 95% confidence interval. The value of Fn was tuned from 1 to 10. AUC, area under receiver operating characteristic curve; CNN, convolutional neural network; Fn, number of features.

these features were difficult to interpret (Table S3). The following three dosimetric features were selected: Dmax, EUD, and V60 (Table S4).

DISCUSSION

The dosimetric features of the esophagus do not fully reflect dose distribution. Several studies have shown that dosimetric factors are predictors of RE, including Dmean,[4] EUD,[23,24] V35,[5] V40,[7] V50,[7,8] and V60.[9,10] A study that considered 533 patients revealed that EUD is a valuable predictor of RE (AUC: 0.66).[23] In another study with 129 patients, EUD was selected as the best predictor of RE (AUC = 0.70).[24] Further, EUD was highly correlated with other dose characteristics, including NTCP, Dmax, Dmean, V60, and V70.[24] Our dosimetric-feature-based model performance was similar to those reported in these two studies. However, predictive capacity was limited owing to the lack of spatial dose information.

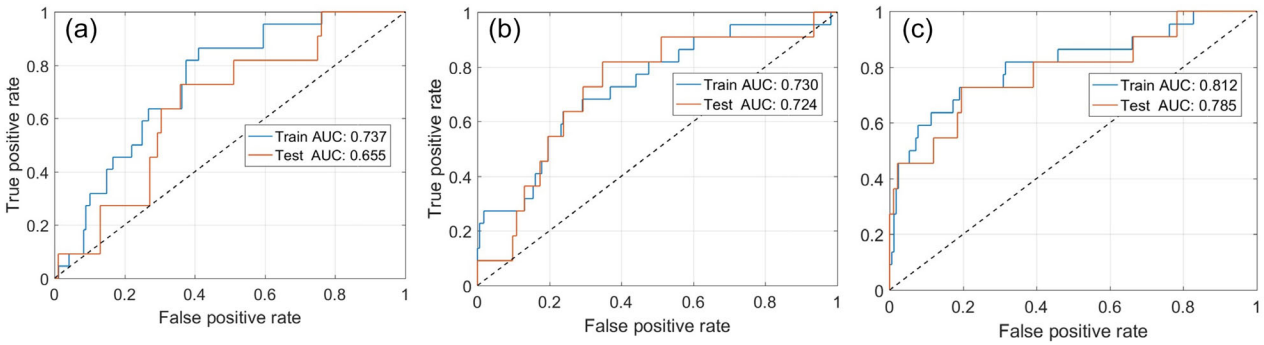

FIGURE 2 ROC analysis. ROC curves of dosimetric features (a), handcrafted features (b), and CNN-extracted features (c) are shown. CNN, convolutional neural network; ROC, receiver operating characteristics.

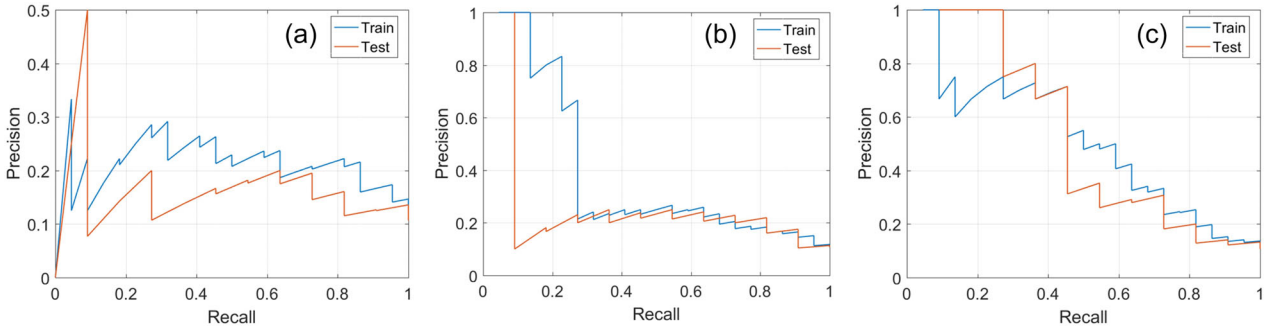

FIGURE 3 Precision-recall curves. Curves of dosimetric (a), handcrafted (b), and CNN-extracted (c) features are shown. CNN, convolutional neural network.

We found that the dosiomic features extracted from the dose distribution outperformed dosimetric features. Other studies have shown that radiation-induced toxicity is related to dosiomic features. Adding 3D dose texture features to dosimetric features improved the prediction of gastrointestinal and genitourinary toxicity in prostate cancer radiotherapy.[16] Dosiomic features were also associated with radiation pneumonitis, with better performance as predictors than dosimetric features.[27,28] Using dosiomic features improves the prediction of early weight loss in lung cancer radiotherapy, which results in better model performance than that of models using dosimetric features.[29] This supports the hypothesis that the predictive ability improves as an increasing quantity of information is extracted from the dose distribution.

The CNN method spares handcrafted feature extraction, and the framework is more general than that of handcrafted features. Our study showed that CNN-extracted features outperformed handcrafted features in RE prediction. Other studies have also demonstrated that the 3D CNN model improved predictive performance in radiation-induced xerostomia[17] and radiation pneumonitis.[22] In our study, improvement due to handcrafted features and CNN-extracted features was probably due to the small volume of the esophagus and its vimineous shape that contained limited subtle information. CNN-extracted features had the highest predictive capability; however, the CNN model was a black box, and the precise meaning of predictors was unclear. This may limit the applicability of the CNN model in clinical practice.

Our study had some limitations. First, the limited sample size could have affected the performance of the prediction model. Second, this study did not include clinical factors associated with RE, such as age and chemotherapy.[30] Third, our study's occurrence rate of symptomatic RE was only 11.6%, which may have affected the prediction model. We tested all combinations of variables with values of 1 to 10, which revealed that models with three handcrafted features or four CNN features performed the best. The model's performance was excellent and comparable to those reported in previous studies, implying successful model construction. Finally, our model only predicted RE; therefore, using findings for treatment plan design and RE prevention requires further investigation.

Prediction models may facilitate the identification of patients at a high risk of developing RE. Both dosiomic prediction models outperformed the dosimetric-feature-based model in predicting RE. CNN-extracted features were more predictive but less interpretable than handcrafted features.

AUTHOR CONTRIBUTIONS

Conceptualization, ZM and ZH; methodology, BL; software, BL; validation, ZM, BL, JD, and ZH; formal analysis, ZM and BL; investigation, ZM; resources, ZM, BL, RW, YL, YB,

MY, YM, JW, LD, YZ, NB, LW, JD, and ZH; data curation, ZM and BL; writing—original draft preparation, ZM; writing—review and editing, ZM, BL, JD, and ZH; supervision, JD, and ZH; project administration, JD, and ZH; funding acquisition, JD, and ZH. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets and codes are available from the corresponding author on reasonable request and only for academic use.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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