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Prediction of response after chemoradiation for esophageal cancer using a combination of dosimetry and CT radiomics

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Abstract

Purpose To investigate the treatment response prediction feasibility and accuracy of an integrated model combining computed tomography (CT) radiomic features and dosimetric parameters for patients with esophageal cancer (EC) who underwent concurrent chemoradiation (CRT) using machine learning.

Methods The radiomic features and dosimetric parameters of 94 EC patients were extracted and modeled using Support Vector Classification (SVM) and Extreme Gradient Boosting algorithm (XGBoost). The 94-sample dataset was randomly divided into a 70-sample training subset and a 24-sample independent test set while keeping the class proportions intact via stratification. A receiver operating characteristic (ROC) curve was used to assess the performance of models using radiomic features alone and using combined radiomic features and dosimetric parameters.

Results A total of 42 radiomic features and 18 dosimetric parameters plus the patients' characteristic parameters were extracted for these 94 cases (58 responders and 36 non-responders). XGBoost plus principal component analysis (PCA) achieved an accuracy and area under the curve of 0.708 and 0.541, respectively, for models with radiomic features combined with dosimetric parameters, and 0.689 and 0.479, respectively, for radiomic features alone. Image features of GlobalMean X.333.1, Coarseness, Skewness, and GlobalStd contributed most to the model. The dosimetric parameters of gross tumor volume (GTV) homogeneity index (HI), Cord Dmax, Prescription dose, Heart-Dmean, and Heart-V50 also had a strong contribution to the model.

Conclusions The model with radiomic features combined with dosimetric parameters is promising and outperforms that with radiomic features alone in predicting the treatment response of patients with EC who underwent CRT.

Key Points

- *The model with radiomic features combined with dosimetric parameters is promising in predicting the treatment response of patients with EC who underwent CRT.*
- *The model with radiomic features combined with dosimetric parameters (prediction accuracy of 0.708 and AUC of 0.689) outperforms that with radiomic features alone (best prediction accuracy of 0.625 and AUC of 0.412).*
- *The image features of GlobalMean X.333.1, Coarseness, Skewness, and GlobalStd contributed most to the treatment response prediction model. The dosimetric parameters of GTV HI, Cord Dmax, Prescription dose, Heart-Dmean, and Heart-V50 also had a strong contribution to the model.*

Keywords Esophageal cancer · Chemoradiation · Treatment outcome · Machine learning

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Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
AUC	Area under curve
CRT	Chemoradiation
CT	Computed tomography
EC	Esophageal cancer
FDG-PET	Fluorodeoxyglucose positron emission tomography
GLCM	Gray-level co-occurrence matrix
GTV	Gross tumor volume
HI	Homogeneity index
ID	Intensity direct
IMRT	Intensity-modulated radiotherapy
NID	Neighbor intensity difference
NR	Non-responsive
OARs	Organs at risk
OS	Overall survival; CR: complete response
PCA	Principal component analysis
RBF	Radial basis function
ROC	Receiver operating characteristic
RS	Responsive
SCC	Squamous cell carcinoma
SVM	Support vector classification
TPS	Treatment planning system
VMAT	Volumetric-modulated arc therapy
XGBoost	Extreme Gradient Boosting algorithm

Introduction

Esophageal cancer (EC) is a very aggressive, lethal malignancy around the world with two different types of disease: squamous cell carcinoma (SCC) and adenocarcinoma, which are predominant in East Asia and western countries, respectively [1, 2]. Currently, definitive chemoradiation (CRT) is considered to be a standard treatment for locally advanced EC. However, the prognosis of patients who received standard CRT is disappointing with greater than 50% of such patients eventually developing recurrence or distant metastases [3, 4].

Dose escalation trials with an intent to irradiate in higher doses to gross tumor volume (GTV) by escalating the dose from standard 50.4 to 64.8 Gy or higher failed to improve overall survival (OS) [5, 6]. This failure was believed to be due to higher toxicities that resulted from dose escalation with conventional radiotherapy technologies [7, 8]. With the advances in radiotherapy technology, EC can be currently treated by intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), or helical tomotherapy to escalate the dose to GTV more precisely with less toxicity to the surrounding normal tissue, which has dramatically reduced morbidity [9, 10]. However, only a few studies have demonstrated that dose escalation schemes can improve local tumor control and lead to better survival for patients with EC treated with modern radiotherapy technology, and the optimal radiation dose should be managed on an individual basis [8].

Evidence exists that there is a positive correlation between OS rate and the histopathological response of patients with who underwent CRT [11, 12]. Patients with a complete response (CR) had a better 5-year OS than those with incomplete response or no response [13]. The ability to predict or assess treatment response at an earlier stage would be of great value in planning individualized dose escalation. Metabolic parameters from fluorodeoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) perfusion parameters demonstrated useful but limited accuracy on treatment response prediction for patients with EC [14–17].

Meanwhile, radiomics extracted from PET and CT images were also extensively investigated as predictors with promising results [18–21]. One limitation of these studies is the limited number of investigated patients. On the other hand, radiotherapy dosimetric parameters, although they affect response, were not included in the studies. The purpose of this study was to evaluate an integrated model using machine learning techniques and combining radiomic features and dosimetric parameters in patients who underwent CRT.

Materials and methods

Patients and treatment

Patients who underwent definitive radiotherapy for primary EC with concurrent chemotherapy between October 2012 and October 2015 were enrolled in this study. Patients were treated with either three-dimensional conformal radiotherapy (3DCRT), or volumetric modulated arc therapy (VMAT), or a combined 3DCRT plus VMAT technique with a prescription dose from 40 to 70 Gy [22, 23]. During the whole course of treatment, patients underwent monthly cisplatin (75 mg/m^2) and 5-fluorouracil (1000 mg/m^2) treatment concurrent with radiation. This retrospective study was approved by the Institutional Review Board of the authors' hospital, and the need for written informed consent was waived.

Response assessment

The response of these patients to treatment was evaluated 3 months after CRT by CT images with contrast and determined based on the cross-sectional changes in maximal wall thickness in axial CT images, as well as in perpendicular primary tumor maximal dimensions. Patients with a 30% or more reduction were classified as responsive (RS), and those with stable or progressive disease (≥ 20% increase) were classified as non-responsive (NR), as shown in Fig. 1.

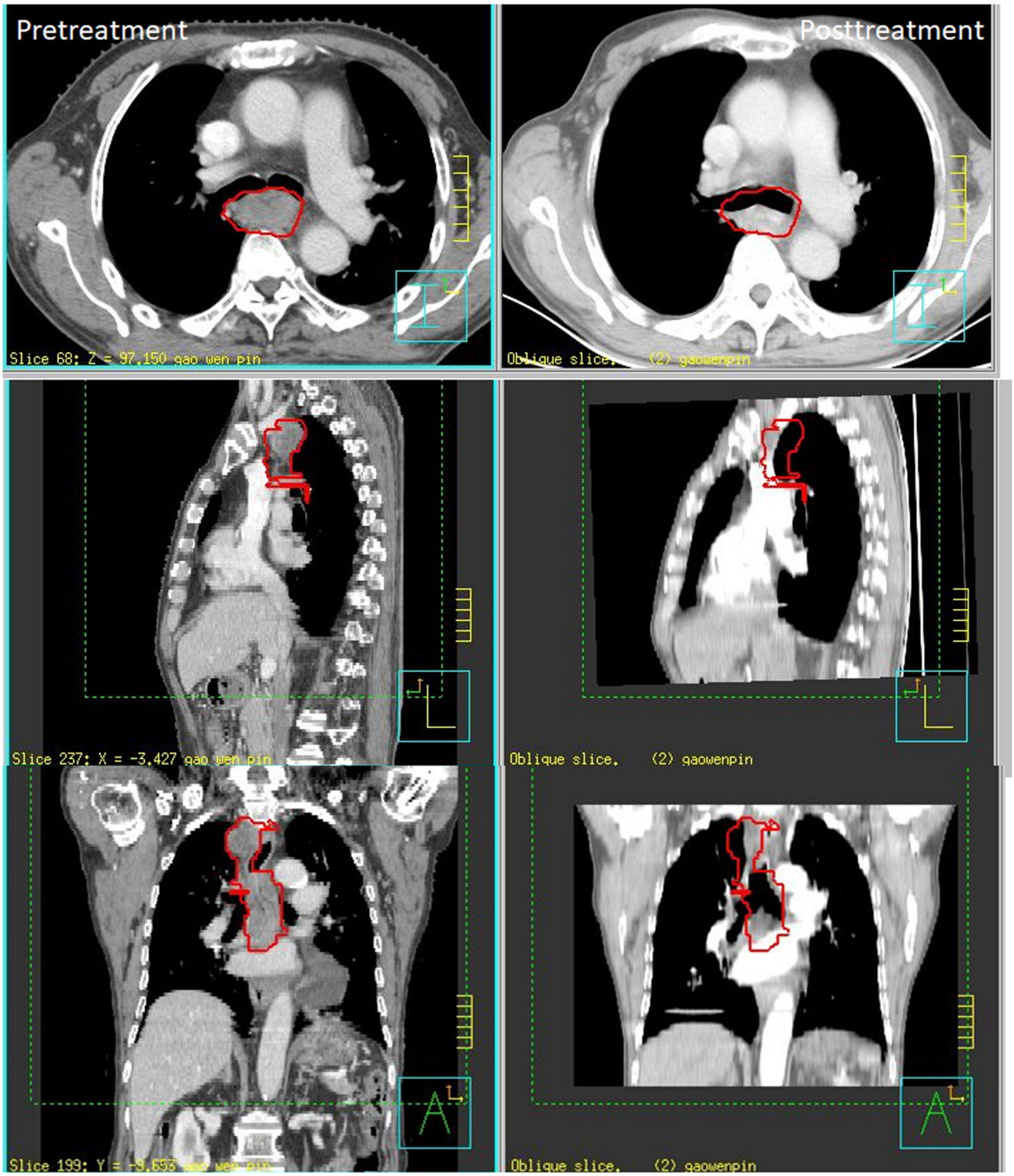

Fig. 1 Typical pretreatment and posttreatment CT images for treatment response evaluation

Imaging and feature extraction

All the patients were scanned by a CT simulator with a 16-detector row (Brilliance, Phillips) under the same clinical protocol: 120 kV, 180–280 mA and a field of view of 500 mm at 3 mm reconstructed section thickness. Iodinated contrast of 100 mL at 300 mg/mL was injected intravenously before the CT scan. The GTV of these patients was delineated by two oncologists who were experts in Pinnacle treatment planning system (TPS) (Philips Medical Systems) with the help from

diagnostic CT, oesophagogastroduodenoscopy, endoscopic ultrasound, and PET scan. DICOM files were exported from TPS to an open infrastructure software platform: IBEX for preprocessing and feature extraction [24]. For each image, we determined 44 radiomic features, grouped into four groups: shape, gray-level co-occurrence matrix (GLCM), neighbor intensity difference (NID), and intensity direct (ID).

Dosimetric parameters

Dosimetric parameters of GTV and organs at risk (OARs) from final composite treatment plans were extracted from TPS using home built MATLAB codes. For GTV, the maximum (Dmax), minimum (Dmin), mean (Dmean) dose, and the volume covered by the prescription dose (V95%) and homogeneity index (HI) were extracted. The Dmax and D2 of the spinal cord, the V25, V30, and V50 (percent volume irradiated by X dose) of the heart, and the V5, V10, V20, V30, and Dmean of the lung were also extracted.

Data processing and statistical analysis

Radiomic features and dosimetric parameters were first visualized using parallel coordinates to investigate their correlation with treatment response [25]. For categorical parameters, such as gender and radiotherapy methods, a number (e.g., 0, 1) was assigned. For numeric features, such as GTV dosage and image texture global median, they were centered by removing the mean value of each feature, then scaled by dividing the standard deviation of each features. This preprocessing makes feature values lie within similar ranges, which reduces the effect of features with large values that may have a larger influence, although this does not necessarily reflect their respective significance.

C-Support Vector Machines (SVM) with Radial Basis Function (RBF) kernel integrated with the LIBSVM library was used in this study. The hyper parameters

Table 1 Patients characteristics of enrolled esophageal cancer patients

Sex	
Male	84 (89.4%)
Female	10 (10.6%)
Tumor location	
Upper	20 (21.3%)
Middle	50 (53.2%)
Lower and/or gastroesophageal junction	24 (25.5%)
Histologic findings	
Adenocarcinoma	1 (1.1%)
Squamous cell carcinoma	92 (97.8%)
Small cell	1 (1.1%)
Histologic grade	
Well	11 (11.7%)
Moderate	37 (39.4%)
Poor	30 (31.9%)
Not specified	16 (17.0%)
T stage	
T1	10 (10.6%)
T2	18 (19.1%)
T3	59 (62.8%)
T4a	3 (3.2%)
T4b	4 (3.3%)
N stage	
N0	52 (55.3%)
N1	25 (26.6%)
N2	17 (18.1%)
M stage	
M0	87 (92.6%)
M1	5 (5.3%)
Mx	2 (2.1%)
Group stage	
I	2 (2.1%)
II	54 (57.4%)
III	26 (27.7%)
IV	12 (12.8%)

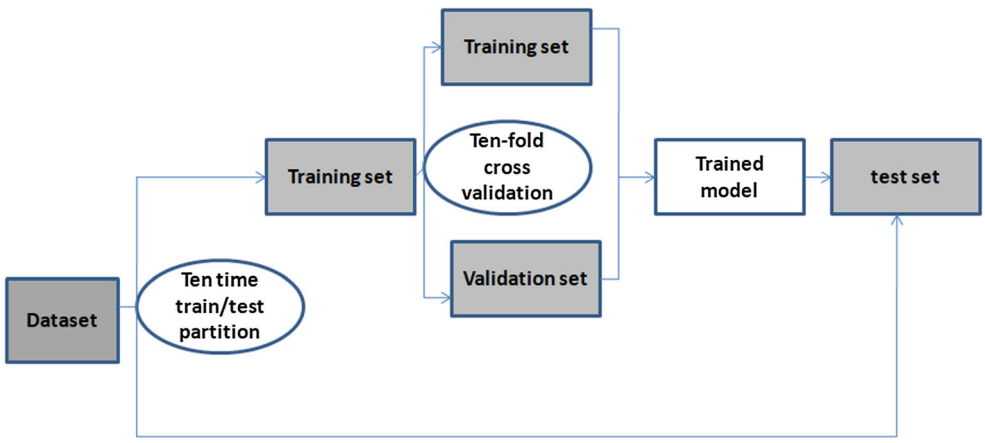

Fig. 2 The procedure to split the dataset and evaluate the model performance

gamma and C of the RBF were chosen based on grid search and cross-validation. SVM is effective in high dimensional feature spaces and its sparse property can inhabit the data noise [26]. The Extreme Gradient Boosting algorithm (XGBoost) was also applied to discriminate the patient prognosis using the scikit-learn libraries. XGBoost has significant advantages in combining a high number of individually weak but complementary tree classifiers to produce a robust estimator [27]. The learning rate of XGBoost was typically set to 0.01, and the maximum depth of a tree was set to 3 to reduce the model complexity. To prevent over-fitting, the subsample was set to 0.8. Another hyper-parameter was optimized by a grid search and cross-validation. To increase the ratio between the number of training sample and the number of features, a Bayesian principal component analysis (PCA) was applied to the training dataset before training XGBoost classifier [28]. The Bayesian formulation of PCA allows the number of principal components to be determined automatically from the data. PCA was used to discover the low rank subspace from the original high feature space, which leads to a higher ratio between the number of training patterns and the number of features, and leads to better generalization properties of the resulting classifier. The XGBoost setting was kept as above to maintain consistency.

The following procedure to split the dataset and evaluate the model performance was followed, as illustrated in Fig. 2. First, the 94-sample dataset was randomly partitioned into a 70-sample training subset and a 24-sample test set while keeping the class proportions intact via stratification. To ensure the distribution of either test or training subsets is representative of the source data, this partition was performed ten times which will lead to multiple models and performance estimates. Second, to build an optimal prediction model, for each training set, various hyper-parameter settings with 10-fold cross-validation were investigated. Then, the hyper-parameter settings that produced the best results to fit the best model on the complete training set were decided. Finally, the ten best models were evaluated on the ten test sets respectively, and the model performances were reported on the average of ten estimates.

Receiver operating characteristic (ROC) curve analysis was used to assess the performance of models using radiomic features alone and using combined radiomic features and dosimetric parameters. An area under the curve (AUC) with a value of 1 indicates an ideal result, whereas values lower than 0.5 means an insignificant result.

Results

Of a total 166 patients who underwent CRT in our institute, 24 patients were irradiated with less than 40 Gy, 30 patients had distant metastasis, and 24 patients were lost to follow-up; these patients were excluded. The study group consisted of a total of 94 patients (male 84; female 10) with a median age of 66 (48–87) years. Most of patients had squamous cell carcinoma (92). The number of patients who had a response to treatment was 58. The other 36 patients had no response or had progressive disease. The patients' characteristics are presented in Table 1.

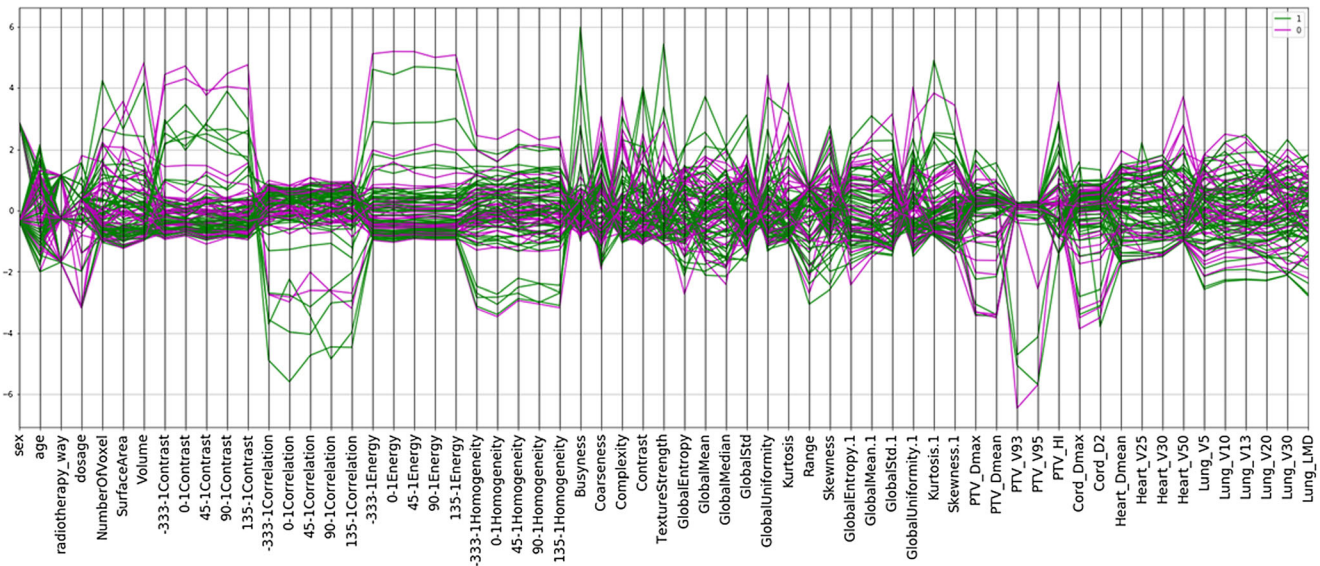

Fig. 3 Data visualization results for all the radiomic features, dosimetric parameters, and patient characteristics with y-axis normalized; prescription dose, GTV, heart- and cord-related dosimetric parameters, as well GlobalMean X.333.1, Correlation, Coarseness, and Skewness are correlated with treatment response

There were total of 42 radiomic features and 18 dosimetric parameters extracted for these 94 cases. Sex, age, and radiotherapy modalities were also included in the modeling. According to the results of data visualization using parallel coordinates, prescription dose, GTV, heart- and cord-related dosimetric parameters, as well GlobalMean X.333.1,Correlation, Coarseness, and Skewness are correlated with treatment response, as shown in Fig. 3. Pearson correlation results shown in Fig. 4 indicated that there was no linear correlation between these parameters and treatment response. Table 2 shows that there was no significant difference on patient characteristics and dosimetric parameters between patients with and without treatment response.

Table 3 shows the prediction accuracy of models generated with SVM, XGBoost and XGBoost plus PCA for radiomic features combined with dosimetric features and radiomic features alone, respectively. XGBoost plus PCA achieved an accuracy of 0.708and an AUC of 0.541 for radiomic features combined with dosimetric parameters, and 0.689 and 0.479 for radiomic features alone, respectively. The ROC curves for comparison between models generated with radiomic features combined with dosimetric parameters and with radiomic features alone are shown in Fig. 5.According to the Gain calculated for each parameter in the prediction model, image features of GlobalMean X.333.1, Coarseness,

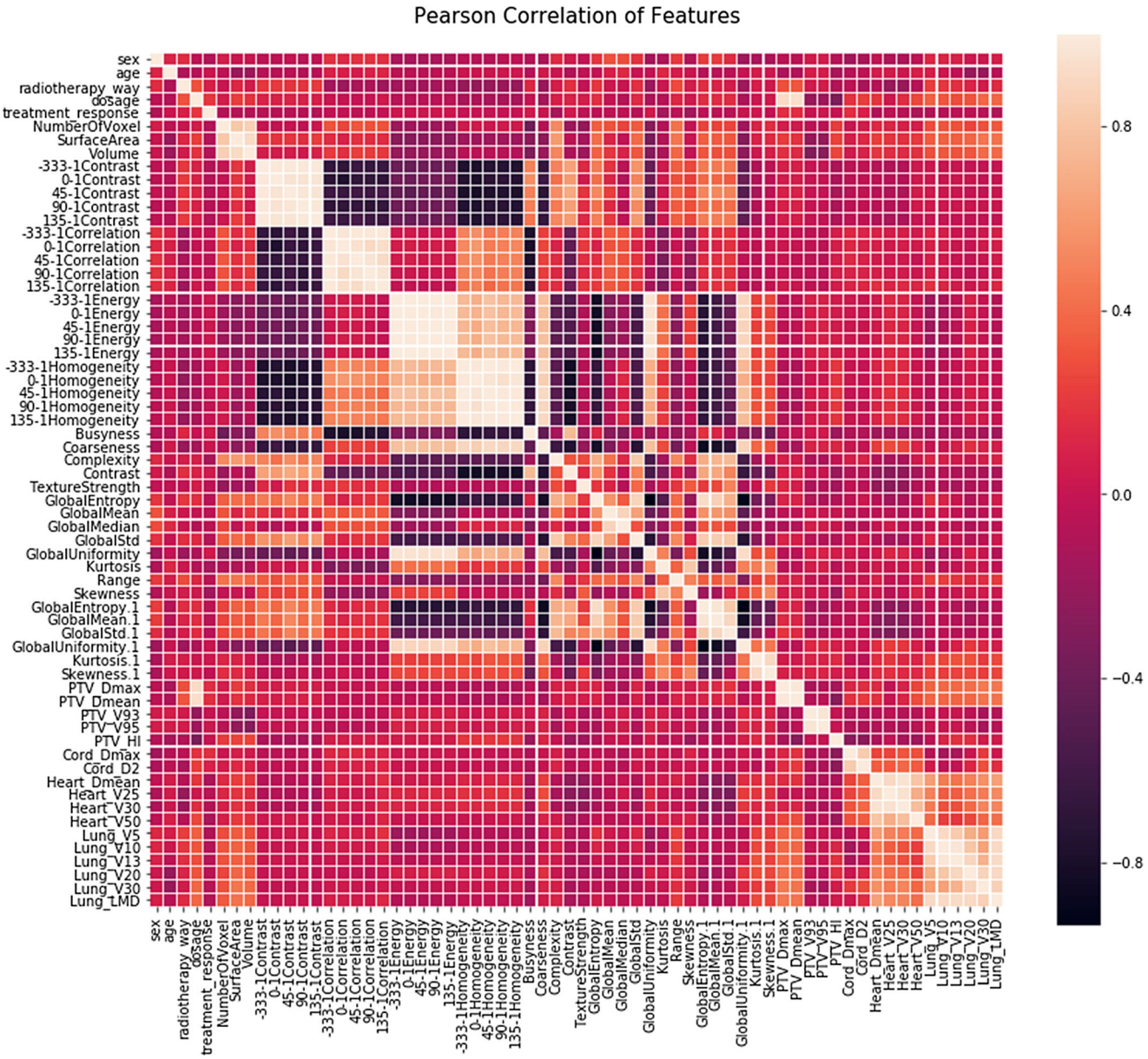

Fig. 4 Pearson correlation heatmap for all the features and parameters; there was no linear correlation between these parameters and treatment response

Table 2 Patients characteristics and dosimetric differences (mean ± standard deviation) between patients with and without response by Student's *t* test

Number of patients	Total (94)	Response (58)	Non-response (36)	*p*
Sex				0.43
Male	84	53	31	
Female	10	5	5	
Age	Median 66 (48–87)	Median 66 (48–87)	Median 65 (48–80)	0.85
Dose (Gy)	56.77 ± 8.51	57.91 ± 6.98	54.95 ± 10.36	0.1
PTV				
Dmax (Gy)	60.81 ± 8.63	61.88 ± 7.50	59.08 ± 10.06	0.13
Dmean (Gy)	57.23 ± 8.00	58.25 ± 6.84	55.59 ± 9.46	0.12
V93 (%)	96.43 ± 14.59	96.34 ± 16.18	96.48 ± 13.66	0.96
V95 (%)	94.99 ± 16.76	95.32 ± 16.07	94.45 ± 18.05	0.81
HI	0.014 ± 0.01	0.014 ± 0.010	0.014 ± 0.010	0.96
Cord				
D2 (Gy)	37.57 ± 9.06	38.24 ± 8.29	36.48 ± 10.22	0.36
Dmax (Gy)	38.42 ± 8.42	39.50 ± 6.97	36.70 ± 10.20	0.12
Heart				
Dmean (Gy)	21.86 ± 12.57	20.77 ± 12.46	23.60 ± 12.73	0.29
V25 (%)	41.65 ± 26.27	40.64 ± 26.23	43.29 ± 26.63	0.64
V30 (%)	36.47 ± 24.76	35.05 ± 24.13	38.75 ± 25.92	0.48
V50 (%)	13.55 ± 13.95	12.32 ± 11.41	15.53 ± 17.27	0.28
Lung				
Dmean (Gy)	11.88 ± 4.25	11.60 ± 4.27	12.32 ± 4.23	0.62
V5 (%)	58.58 ± 22.86	56.77 ± 61.49	61.49 ± 23.65	0.33
V10 (%)	38.96 ± 16.90	38.07 ± 16.73	40.39 ± 17.31	0.52
V13 (%)	30.81 ± 13.59	30.26 ± 13.48	31.69 ± 13.90	0.62
V20 (%)	19.47 ± 8.47	19.17 ± 8.65	19.96 ± 8.25	0.67
V30 (%)	11.73 ± 5.66	11.50 ± 5.65	12.11 ± 5.72	0.62

Skewness, and GlobalStd contributed most to the model. The dosimetric parameters of GTV HI, Cord Dmax, Prescription dose, Heart-Dmean and Heart-V50 also had a strong contribution to the model.

Discussion

In this study, the model combining radiomic features and dosimetric parameters for patients with EC who underwent concurrent CRT achieved a prediction accuracy of 0.708. We also found that CT image features of GlobalMean X.333.1, Correlation, Coarseness, and Skewness were correlated with treatment response of EC patients. Skewness and kurtosis were previously reported to differentiate stable disease from partial response for EC patients treated by CRT [21]. Ganeshan et al demonstrated that tumor heterogeneity evaluated with CT texture features in 21 EC patients had the potential to provide a marker for tumor aggression and prognosis [29]. Yip et al also reported that changes in CT texture feature before and after neoadjuvant chemotherapy in 31 EC patients were associated with treatment response and survival [30].

In this study, dosimetric parameters of GTV HI, Cord Dmax, Prescription dose, Heart-Dmean and Heart-V50 had a strong contribution in predicting the treatment response. However, treatment modalities, such as conformal radiotherapy, VMAT, and combined conformal and VMAT technique were not significant factors in predicting the treatment. Radiation dose to the target volume and unnecessary dose to surrounding normal tissues were major concerns during EC radiotherapy. Dose escalation to target volume has been extensively investigated since the dose delivered to the target tumor volume affects the primary

Table 3 Prediction accuracy and AUC values for models with all the features and models with radiomic features only

	Radiomic features + dosimetric parameters		Radiomic features	
Algorithm	Accuracy	AUC	Accuracy	AUC
SVM	0.666	0.361	0.625	0.412
XGBoost	0.625	0.563	0.500	0.513
XGBoost + PCA	0.708	0.689	0.541	0.479

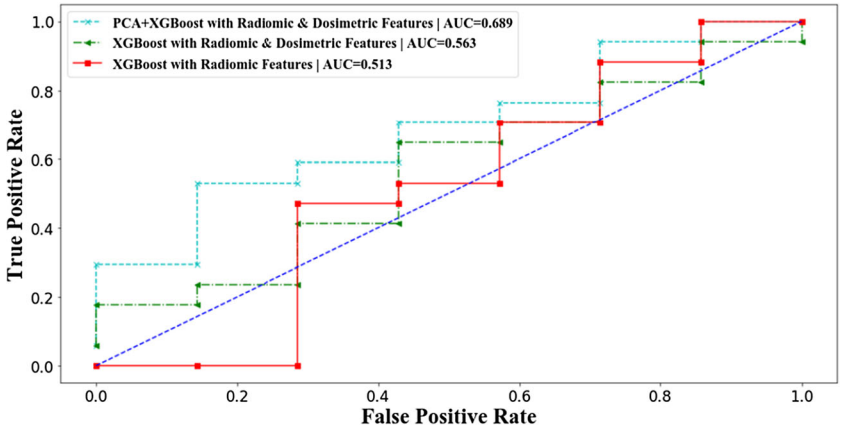

Fig. 5 Receiver operating characteristics curve and area under curve values for models generated by XGBoost and XGBoost plus principle component analysis with radiomic features combined with dosimetric parameters, and for radiomic features alone

treatment response of tumors [6]. Decreasing the dose to normal tissues by using modern radiotherapy techniques is also critical for the patients' treatment response and survival [31].

Combining dosimetric parameters and radiomic features in the prediction model improved the performance. As shown in Table 3, radiomic features alone showed the best prediction accuracy of 0.625 and AUC of 0.412, compared with the prediction accuracy of 0.708 and AUC of 0.689 with the combined model. Previously, radiomic features from pretreatment contrast-enhanced CT images demonstrated high AUCs (0.686–0.727) in differentiating responders from non-responders with limited number of EC patients who underwent CRT [21].

To suppress the risk of over-fitting and bias in this study, we adopted two methods to make the best use of limited patient data. First, a probabilistic PCA was built to reduce the feature dimension. It is well known that a lower-dimensional data will improve the model predictive performance under the circumstances of scarce data. Second, a 10-fold cross-validation procedure was used to find the model parameters that lead to best model performance. This procedure allows us to make use of all of the training data to evaluate the model performance, thereby avoiding the relatively noisy estimate of performance when data is scarce. A major advantage of cross-validation is that it does not waste too much data where sample is small with a computational time increase.

One limitation of the current study is that the treatment response was evaluated with morphological changes of the tumor, rather than by histopathological analysis. However, an accurate method of determining true pathological complete response for EC is still lacking [32]. Another limitation of this study is that nearly all the EC patients enrolled had squamous cell carcinomas. The prediction of treatment response demonstrated in this study may not apply to adenocarcinoma. Finally, this is a retrospective study from a single center with a relatively small number of patient, and therefore these findings should be considered as preliminary, pending validation.

In summary, a model combining radiomic features and dosimetric parameters outperformed that of radiomic features alone in predicting treatment response in EC patients who underwent CRT.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Congying Xie.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise: Cong Liu.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- observational
- performed at one institution

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