# CT-based Radiomic Analysis for Prediction of Treatment Response of Salvage Chemoradiotherapy for Loco-regional Lymph Node Recurrence After Curative Esophagectomy

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# Abstract

**Objective:** To investigate the capability of computed tomography (CT) radiomic features to predict the therapeutic response and local control of the loco-regional recurrence lymph node (LN) after curative esophagectomy by chemoradiotherapy (CRT).

**Methods:** This retrospective study included 129 LN from 77 patients (training cohort: 102 LN from 59 patients; validation cohort: 27 LN from 18 patients) with postoperative esophageal squamous cell carcinoma (ESCC). The region of the tumor was contoured in pretreatment contrast-enhanced CT images. The least absolute shrinkage and selection operator (LASSO) with logistic regression was used to identify radiomic predictors in the training cohort. Model performance was evaluated using the area under the receiver operating characteristic curves (AUC). The Kaplan-Meier method was used to determine the local recurrence time of cancer.

**Results:** Seven features were selected to construct a radiomics model for predicting therapeutic response. The AUCs in the training and validated cohorts were 0.777 (95%CI: 0.667−0.878) and 0.765(95%CI: 0.556−0.975), respectively. A significant difference of radiomic score (Rad-score) between the response and non-response was observed in the two cohorts ($P < 0.001$, 0.034, respectively). Two features were identified for classifying whether to relapse in two years. AUC was 0.857(95%CI: 0.780−0.935) in the training cohort. The local control time of the high Rad-score group was higher than the low group in both cohorts ($P < 0.001$ and 0.025, respectively). After the Cox regression analysis, the Rad-score indicated high-risk factors for local recurrence within two years.

**Conclusions:** The radiomics approach can be used as a potential imaging biomarker to predict treatment response and local control of recurrence LN in ESCC patients.

# Introduction

Esophageal cancer ranks seventh in terms of incidence and sixth in overall mortality worldwide [1]. The incidence of esophageal cancer ranks five in China and it is the fourth leading cause of cancer-related deaths in China, and 90% of esophageal carcinoma patients are diagnosed with esophageal squamous cell carcinoma (ESCC) [2]. Surgical resection is the mainstay for potentially curable esophageal cancer, but lymph node (LN) recurrence after surgery is one of the main types of treatment failures [3, 4]. The prophylactic therapy is found effective in the T3−4 or N1−3 post-resection pathological stage [5−7]. But some patients who failed to receive adjuvant treatment due to developing postoperative complications or refusal to take treatment reported LN recurrence soon after surgery. For T1−2 N0 M0 cancer patients, postoperative follow-up was done, but some patients developed loco-regional LN recurrence within two years because of tumor heterogeneity and underestimated staging [8]. The salvage chemoradiotherapy (CRT) remarkably improved the survival rate of these patients, and the patients who were sensitive to CRT had a longer survival time than the patients insensitive to CRT [9−11]. Prediction of the efficacy of CRT on recurrent lymph nodes (RLNs) remains a challenge.

Radiomics refers to the high-throughput extraction of quantitative data from medical images and then mining of correlations between different features for the diagnosis/prognosis of the disease. After first proposed in 2012 [12, 13], radiomics has attracted widespread attention of researchers worldwide because it is a non-invasive, quantitative, and low-cost approach and has shown promise in the prediction of differentiation between malignant and other tissues, tumor staging, and treatment response [14, 15]. Several studies have focused on predicting preoperative staging of esophageal cancer and evaluating the response of chemoradiotherapy [16–18], though fewer studies have used radiomics to predict the response in loco-regional RLN after esophagectomy treatment by salvage radiochemotherapy.

In this study, we aimed to build the radiomics signature to assess therapeutic response and local control of salvage radiotherapy (RT) or CRT for LN recurrence after curative esophagectomy.

# Materials And Methods

## Patients

A total of 129 metastatic lymph nodes from 77 patients with postoperative ESCC were investigated in the current retrospective study. The study was approved by the ethics committee of Taixing People's Hospital, Jiangsu, China. Prior written informed consent was obtained from each of the study participants. The salvage CRT or radiotherapy (RT) was administered to the ESCC patients with lymph node recurrence post-surgery from January 2015 through December 2016 at the Department of Radiotherapy of Taixing People's Hospital in Jiangsu Province, China. We followed the following inclusion criteria for the selection of participants:

(a) Patients received curative esophagectomy and pathologically confirmed SCC; not received radiotherapy treatment either prior or postoperatively;

(b) The lymph node recurrences located within the bilateral supraclavicular region and mediastinum; the diagnostic approaches for lymph metastasis included physical examinations, B-mode ultrasound, computed tomography (CT) of the supraclavicular and thoracic region, positron emission tomography (PET)-CT and histological confirmation through biopsy;

(c) No clear contraindications to radiotherapy and chemotherapy, and no distant metastases such as heart, brain, lung, and bone; and

(d) Detailed follow-up information of patients within three years available.

Overall, 85 consecutive patients were enrolled, after exclusion, 77 were considered. The exclusion criteria were as follows:

(a) The information of follow-up was poor ($n = 5$);

(b) The radiotherapy treatment was administered after esophagectomy ($n = 2$);

(c) The pathology was not SCC ($n = 1$).

According to the 7th edition of American Joint Committee on Cancer (AJCC) staging, 129 lymph nodes of 77 patients were included in the study, of which 47 patients had a single lymph node metastasis, and 30 patients reported two or more lymph node metastases. The patients were randomly assigned to the training cohort and validation cohort in a ratio of about 10:3. In the training cohort, models were built and then were validated in the validation cohort. The clinic characteristics of patients in both cohorts are presented in Table 1.

Table 1
Characteristics of patients in training and validation cohorts

| Characteristics | Training cohort | Validation cohort | P | Summary |
|---|---|---|---|---|
| Number of patients | 59 | 18 | | 77 |
| Number of LN | 102 | 27 | | 129 |
| Gender | | | | |
| Female | 9 | 5 | 0.295 | 14 |
| Male | 50 | 13 | | 63 |
| Age (Median (range)) | 64 (46−79) | 64 (50−74) | 0.433 | 64 (46−79) |
| Number of LN per patient | | | | |
| Single | 36 | 11 | 0.778 | 47 |
| ≥ 2 | 23 | 7 | | 30 |
| T stage | | | | |
| T1 + 2 | 26 | 11 | 0.159 | 37 |
| T3 + 4 | 33 | 7 | | 40 |
| N involved | | | | |
| N⯑ | 29 | 8 | 0.792 | 37 |
| N- | 30 | 10 | | 40 |
| Median LN recurrence time (month (range)) | 11 (1−72) | 18 (5−60) | 0.138* | 11 (1−72) |
| POCT | | | | |
| YES | 24 | 7 | 0.559 | 31 |
| NO | 35 | 11 | | 46 |
| CRT for LN | | | | |
| YES | 40 | 9 | 0.262 | 49 |
| NO | 19 | 9 | | 28 |
| Median radiation dose (Gy (range)) | 60 (50−64) | 60 (50−64) | 0.194 | 60 (50−64) |
| Treatment response | | | | |
| response (CR + PR) | 75 | 18 | 0.148 | 93 |

| Characteristics | Training cohort | Validation cohort | P | Summary |
|---|---|---|---|---|
| nonresponse (SD + PD) | 27 | 9 | | 36 |
| Median control time of LN (month (95%CI)) | 13.0 (11.5–14.4) | 12.0 (9.3–14.7) | 0.109* | 13.0 (11.9–14.0) |

Note:

$\chi^2$ test and Fisher's exact test for categorized variables; two-sample $t$-test for continues variables

* log-rank test

Abbreviations: LN, lymph node; +, metastasis positive; - metastasis negative, CRT: Concurrent chemoradiotherapy

POCT: Postoperative adjuvant chemotherapy

## Chemo-radiotherapy (CRT)

All patients received three-dimensional conformal radiation therapy (3DCRT). The gross tumor volume (GTV) was defined as recurrent lymph nodes identified by CT scans or PET/CT. The clinical target volume (CTV) was defined as GTV with a 0.5 cm to 1.5 cm expansion range. The planning tumor volume (PTV) was ascertained by adding 0.5 cm radially to the CTV. A total dose of 50−64 (median, 60) Gy was delivered in 2 Gy per fraction five days a week. Also, twenty-eight patients received radiation therapy alone; forty-nine patients received CRT of TP (paclitaxel, 135 mg/m$^2$ on day 1 and cisplatin, 25 mg/m$^2$ on days 1−3, 28 days per cycle). According to toxicity levels, the dose adjustment was implemented in the second chemotherapy cycle in ten patients.

## Treatment evaluation and follow-up

One month after the completion of the treatment, the therapeutic response was assessed using CT image with contrast, according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1) [19]. Patients with complete response (CR) or partial response (PR) were considered responders, while those with stable disease (SD) or progressive disease (PD) were classified as non-responders. The patients were followed at 1-or 3-month intervals by a history and physical examination, ultrasonography, and computed tomography after the completion of therapy. Local-regional failure time was calculated from the end of the first chemoradiotherapy or radiotherapy to the time of the second recurrence.

## Image acquisitions and tumor segmentation

All patients underwent contrast-enhanced CT of the chest performed using a 64-channel multi-detector CT scanner (LightSpeed VCT, GE Medical Systems, Milwaukee, WI, USA) in our hospital between January 2015 and December 2016. The acquisition parameters were as follows: 120 kV; 160 mAs; 0.4 s or 0.5 s

rotation time; detector collimation, 64 × 0.625 mm or 64 × 1.25 mm; the field of view, 350 mm × 350 mm; and matrix, 512 × 512. The contrast-enhanced CT was performed after a 25-second delay following intravenous administration of 85 mL of iodinated contrast material (Iohexol injection; Yangtze River Pharmaceutical Group, Jiangsu, China) at a rate of 3.0 mL/s with a pump injector. All the CT images were reconstructed with a standard kernel. These CT images were retrieved from the picture archiving and communication system (PACS).

Regarding the radiotherapy plan in the treatment planning system and AJCC 7th edition staging, two radiation oncologists with > 5 years of experience in interpreting esophageal carcinoma radiology outlined the metastatic lymph nodes in the clavicle, and mediastinal lymphatic drainage area performed manual segmentation of the metastatic lymph nodes on each patient's CT images. 3D-slicer (https://www.slicer.org/), an open-source and free software platform for biomedical research [20], was employed for this task. These regions-of-interest (ROIs) were used in subsequent feature extraction for further analysis.

## Radiomics feature extraction

Pyradiomics (http://pyradiomics.readthedocs.io/), an extension in 3D-slicer (version 4.8.1), is an open-source Python package for the extraction of radiomics features from CT imaging [21]. There were 106 features: 13 shape-based, 18 first-order, 24 Gray Level Co-occurrence Matrix (GLCM), 16 Gray Level Size Zone Matrix (GLSZM), 5 Neighboring gray-tone difference matrix (NGTDM), 14 Gray-level dependence matrix (GLDM) and 16 Gray Level Run Length Matrix (GLRLM) features (see Additional file 1: Supplementary Table S1). The ROIs were manually delineated slice-by-slice by two expert radiologists (Readers 1 and 2, with clinical experience of 10 and 8 years, respectively, in esophageal cancer radiotherapy). Reader 1 delineated the ROI again a month later. Reader 2 manually sketched the ROIs only once. The inter-class correlation coefficient (ICC) was used to determine the agreement in feature values between the observers. In our study, radiomic features with ICC greater than 0.75 were extracted, and reader 1 delineated some ROIs for the first time for further study.

## Statistical analysis

All statistical analyses were performed on R software (version 3.5.3, http://www.r-project.org/). The difference in the categorical variables between the two groups was assessed with the two-sample $t$-test, chi-square test, or Fisher's exact test as appropriate. The Kaplan-Meier method and log-rank test were used to estimate disease-free survival (DFS). Multivariate analyses were performed using the Cox proportional-hazards model. The least absolute shrinkage and selection operator (LASSO) with logistic regression was applied to identify optimal predictors in the training cohort by the "glmnet" package. The "ggplot2" and "pROC" packages were employed to draw ROC curves and evaluate the model performance by the AUC. The "survival" and "survminer" packages were used for survival analysis and to draw survival cures. A two-sided $p$-value of < 0.05 was considered statistically significant.

# Results

## The radiomics model for therapeutic response

The response rate of the metastatic lymph nodes in this study was 73.5% (75/102) in the training cohort and 66.7% (18/27) invalidation cohort, respectively ($p = 0.148$). No clinical differences were found between the training cohort and the training cohort (Table 1). The LASSO (54) with logistic regression was used to select the most significant radiomics features for therapeutic response in the training cohort (Fig. 1), and ultimately seven features were identified. The radiomic score (Rad-score) was calculated by these radiomics features (Table 2). The Rad-score in the training cohort were $1.243 \pm 0.433$ and $0.698 \pm 0.433$ for response and non-response, respectively ($P < 0.001$). A statistically significant difference in Rad-score in the validated cohort was also observed ($1.303 \pm 0.566$ vs. $0.816 \pm 0.451$, $P = 0.034$). The AUCs in the training cohort and validated cohort were 0.777 (95%CI: 0.667−0.878) and 0.765 (95%CI: 0.556−0.975), respectively (Fig. 1).

Table 2
Coefficients and features of seven radiomic signatures for response

| Coefficients | Features |
|---|---|
| -3.215941 ($\beta_0$) | Constant |
| -0.4714669 ($\beta_1$) | Shape-Sphericity ($\chi_1$) |
| 1.627270 ($\beta_2$) | Glcm-Inverse Variance ($\chi_2$) |
| 0.03268378 ($\beta_3$) | First order-Interquartile Range ($\chi_3$) |
| 0.01575666 ($\beta_4$) | First order-90 Percentile ($\chi_4$) |
| 0.003081561 ($\beta_5$) | First order-Kurtosis ($\chi_5$) |
| 2.5310139 ($\beta_6$) | Glrlm-Short Run Emphasis ($\chi_6$) |
| $2.987626^{\wedge}10^{-9}$ ($\beta_7$) | Glszm-Large Area High Gray Level Emphasis ($\chi_7$) |

## The radiomics model for 2-year local control rate

In the training cohort, the 12 metastatic lymph nodes, taken from seven patients who died within two years, were excluded because no local recurrence was observed. Finally, 90 lymph nodes were used to build a radiomics model to predict two years of local recurrence. The 2-year control rate is 25.5% (23/90). First, we considered that whether recurrence occurred within two years was as a binary variable, then we used the LASSO (9) to select the most significant radiomics features for classifying whether to relapse. At last, two features were identified (Fig. 2), and the Rad-score of the 2-year local control rate (Rad-score-2-year) was determined using the following equation:

Rad-score-2-year = − 3.281461437 + 0.002394247* (First order-Interquartile Range) + 3.434397106* (Glrlm-Run Percentage)

The AUC of the Rad-score-2-year in the training cohort composed of ninety lymph nodes was 0.857 (95%CI: 0.780–0.935). When the cutoff value was − 1.015, the specificity was 0.716, and the sensitivity was 0.870. Rad-score-2-year greater than the cutoff value was presumed to be a high Rad-score. Otherwise, it was a low Rad-score. Considering Rad-score high and low as a layering factor, the local control rate of the high Rad-score group was higher than that of the low Rad-score group both in the training and the validation cohorts, with $p$-values of < 0.001 and 0.025, respectively (Fig. 2).

In order to further determine the relationship between the Rad-score and the local control of lymph nodes for two years, 102 lymph nodes (including the training set and verification set) were further divided into a 2-year local control group and a 2-year local uncontrolled group according to the local control situation within two years. On comparison of clinical characteristics of two groups, we observed that the T staging, radiation dose, treatment response, and Rad-score-2-year were statistically different ($P$ = 0.005, 0.01, < 0.001, < 0.001, respectively) (see Additional file 1: Supplementary Table S2), and concurrent chemoradiotherapy was a critical state ($P$ = 0.071). After Cox regression analysis of the above five factors, we found that the treatment response and Rad-score-2-year were high-risk factors for local recurrence within two years, as shown in Fig. 3.

## Discussion

Radiomics can provide a digital and modeling method to predict the effect of the tumor to radiotherapy or chemotherapy by high-throughput extraction of quantitative information from medical images. It has been studied in lung cancer, prostate cancer, breast cancer, and other tumors [22–27]. There are also some studies in esophageal cancer [18, 28–31]. Zhen et al. [31] noticed that five features of contrast-enhanced CT images discriminated non-responders from responders (AUCs from 0.686 to 0.727) in esophageal carcinoma. Yang et al. [18] postulated three predictive models using radiomic parameters for pCR after neoadjuvant chemotherapy and radiation therapy (nCRT) in ESCC (AUC, 0.84–0.86 in training cohorts and 0.71–0.79 in testing cohorts). Beukinga et al. [32] constructed the prediction model by combining ^{18}F-FDG PET radiomics and clinical T-stage in predicting pathologic complete response to nCRT and AUC was 0.81. Many studies have highlighted the primary lesions of the esophagus, but this study focused on the recurrence of lymph nodes post-surgery in esophageal cancer. We used a CT radiomic model to predict its response to RT or CRT. The seven features were selected by LASSO with 10-fold cross-validation, including one each shape-based features, GLCM, GLRLM, and GLSWZM, three first-order features. The AUCs were 0.777 and 0.765 in the training and validated cohort, respectively, similar to the previous findings. Although the microenvironment and heterogeneity of tumor metastasis are different from those of the primary lesion and the response to treatment is also different [33], this study establishes that CT-based radiomics can still predict its therapeutic response. Local recurrence within two years is still one of the principal reasons for the progression in these patients [10, 34]. Hence, we used the radiomic model to predict the 2-year local control rate. At last, two features were chosen by LASSO with 5-

fold cross-validation, and AUC was 0.857 in the training cohort. Due to the low 2-year local control rate (25.93%) in this study and the small number of cases ($n = 27$) in the verification cohort, only five lymph nodes could be controlled over two years. The AUC method is not a good way to calculate the predictive ability of the model in the validated cohort. Therefore, we used the level of Rad-score-2-year as a risk factor to create a local recurrence time curve, despite a $p$-value of less than 0.05 in the training group or the validated group. Cox regression analysis revealed that Rad-score-2-year is a high-risk factor for local recurrence in two years in the current study. We employed different methods to explore the relationship between the CT-based radiomic model and the efficacy of mediastinal metastatic lymph nodes on radiotherapy or chemoradiotherapy. For patients with poor results, other treatment options such as immunotherapy [35] were considered.

Several studies have revealed contradictory results on whether tumor size or volume is considered as a risk predictor for response [10, 18, 36, 37]. Yang et al. [18] argued that the tumor volume could not predict pathologic complete response (pCR) in any of the patients in their cohort, but they documented that the surface volume ratio (surface area to volume ratio, a lower SVR indicates a more compact shape) might provide more information about pCR than tumor volume. In our study, we also noticed that Shape-Sphericity (a measure of the roundness of the shape of the tumor region relative to a sphere, in Table 2) was related to the response of metastatic lymph nodes to RT or CRT. The tumor heterogeneity was correlated with tumor proliferation, necrosis, and hypoxia and may be correlated to poor response and worse prognosis [38]. The texture-based features exhibited the spatial arrangement of the voxels and disclosed the change of local intensity in the tumor region [39]. The emerging evidence suggests that image-based quantification of tumor heterogeneity may provide important information for predicting response to treatment and predicting prognosis in esophageal cancer patients [32, 40, 41]. The GLCM entropy was the most often reported radiomic feature, reflecting the local randomness (irregularity) within the image, and where low GLCM entropy represents a more homogeneous texture [41]. The model of therapeutic response in the current study contained GLCM-Inverse Variance, another measure of the local homogeneity of an image. Yip et al. [42], in their study, noticed the pretreatment and posttreatment standard deviation of a histogram showing a borderline association with pathological tumor response. A proportional change in skewness < 0.39 was associated with improved survival. Hou et al. [31] highlighted that histogram skewness, histogram kurtosis, and GLSZM long-zone emphasis discriminated non-responders from responders using an artificial neural network-derived prediction model in 49 patients. In our study, the prediction model for 2-year local control rate contained two texture-based features, First-order-Interquartile Range (the range of gray values)and GLRLM-Run Percentage (the coarseness of the texture by taking the ratio of several runs and number of voxels), both indicating the heterogeneity of the tumor. We constructed the multi-parameter prediction model to improve the predictive value of the multiple feature combination; however, nine features were found related to tumor heterogeneity, with only one feature reflecting the shape of the tumor. It suggested that the heterogeneity of the tumor is related to treatment effect and survival. This is similar to many other CT-based radiomic model [18, 29].

Limitations: This study has certain lacunae. First, we only applied basic radiomic features, overlooking the Laplacian of Gaussian (LOG) filter approach, which could be able to reduce image noise and highlight

different anatomical spatial scales within the tumor [30]. Second, this was a retrospective study with a small size of the, and the data were derived from the same institution. Our results should have been validated in multiple centers with a larger and prospective patient cohort in the future.

# Conclusions

Overall, in this study, we constructed a CT-based radiomic model to predict the efficacy of salvage RT or CRT for LN recurrence after curative esophagectomy. The proposed model demonstrated a strong prognostic value. Therefore, as a non-invasive and quantitative method, the radiomics approach can be employed as the potential imaging biomarker for clinical practice in the prediction of treatment response and local control to salvage RT or CRT for LN recurrence in patients with ESCC. Overall, it is suggested to further study and fine tune the radiomic model by this approach to improve predictive performance through larger wider multicentric meta-studies.

# Abbreviations

ESCC: Esophageal squamous cell cancer; LN: lymph node; CRT: chemoradiotherapy; RLNs: recurrent lymph nodes; RT: radiotherapy; CT: computed tomography; PET: positron emission tomography; POCT: Postoperative adjuvant chemotherapy; AJCC: American Joint Committee on Cancer; CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; LASSO: Least absolute shrinkage and selection operator; ROC: Receiver operating characteristic; AUC: Area under the receiver; 3DRT: Three-dimensional conformal radiation therapy; GTV: gross tumor volume; CTV: clinical target volume; PTV: planning target volume; ROIs: regions-of-interest; GLCM: Gray-level co-occurrence matrix; GLSZM: Gray-level size-zone matrix; GLRLM: Gray-level run-length matrix; NGTDM: Neighboring gray-tone difference matrix; GLDM: Gray-level dependence matrix.

# Declarations

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interests

Authors declare that there is no competing interests.

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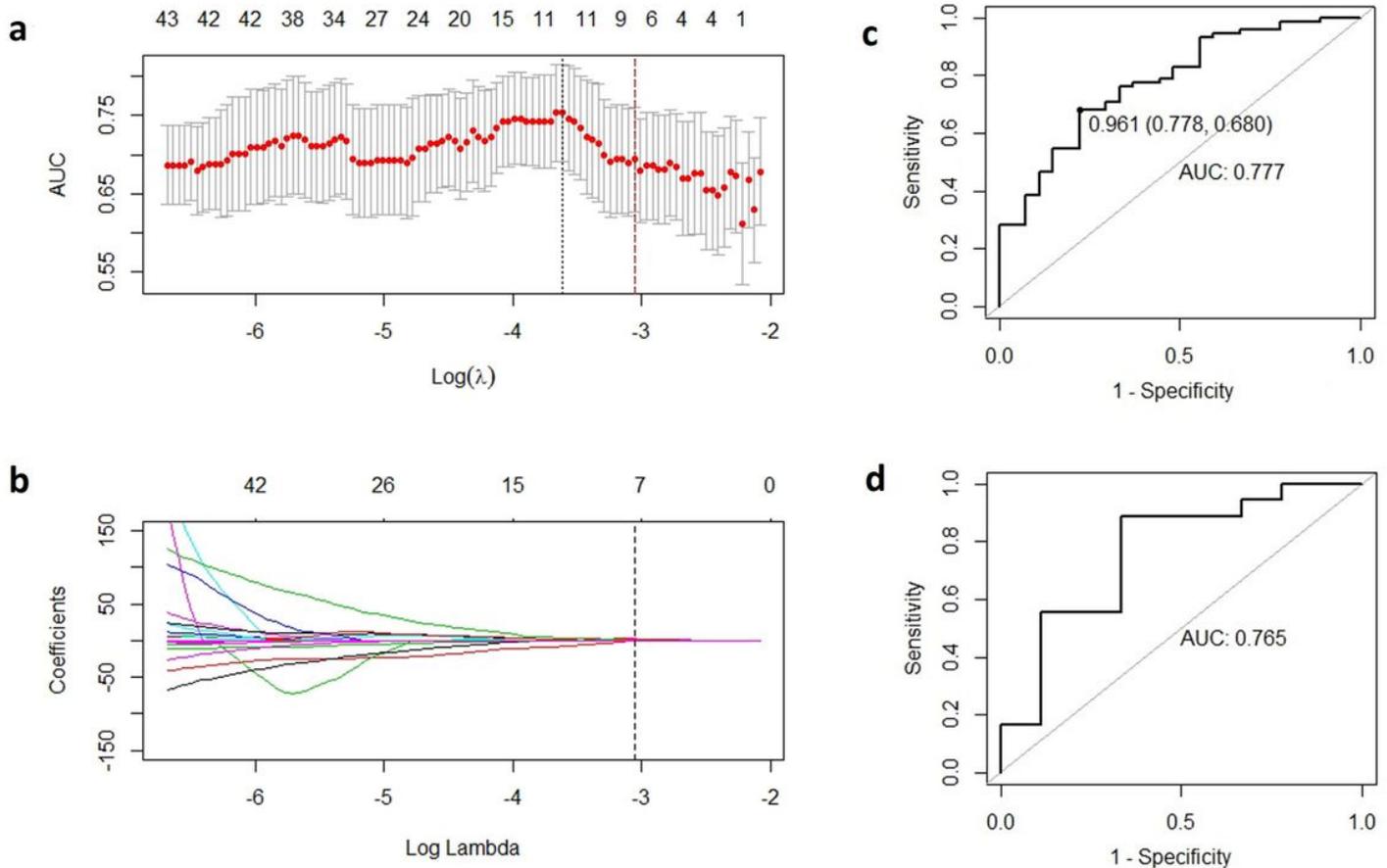
# Figures



## Figure 1

Radiomics feature selection using the least absolute shrinkage and selection operator (Lasso) logistic regression model. (a) The cross-validation curve. The area under the receiver operating characteristic (AUC) curve was plotted versus log (Lambda). Red dotted vertical lines were drawn at the optimal value by using 10-fold cross-validation and the 1 standard error of the minimum criteria (the 1-SE criteria). (b) Shows the coefficient profiles of 106 radiomics feature. The vertical dotted line was drawn at the value selected in (a). The Lambda value of 0.0471, with Log(Lambda) = -3.056 was chosen, and 7 nonzero coefficients were selected. (c, d) Receiver operating characteristic (ROC) curves for Rad-score in training and validated cohort. When the cutoff value was 0.961, the specificity was 0.778 and the sensitivity was 0.680.
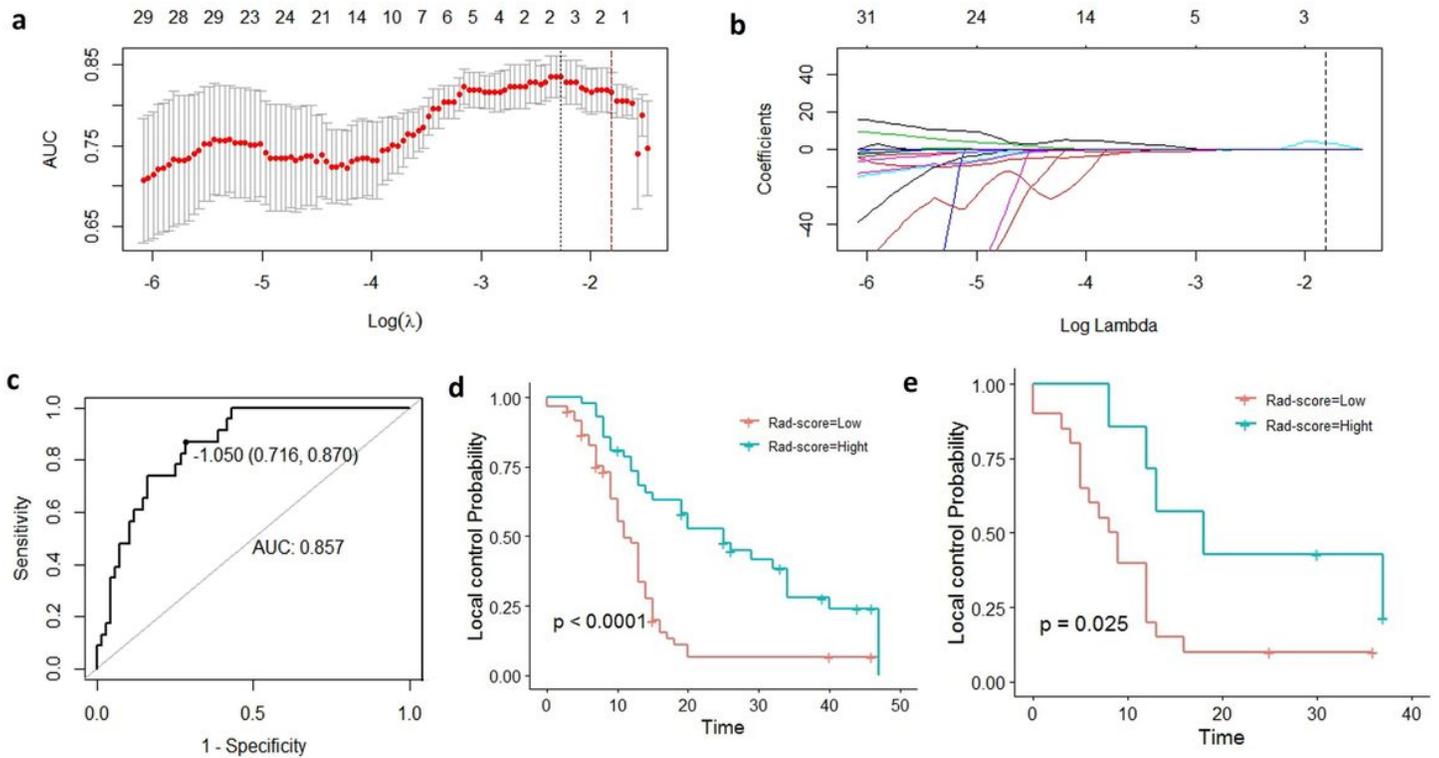
## Figure 2

Radiomics feature selection using the Lasso logistic regression model. (a) The AUC cross-validation curve was plotted versus log (Lambda). Red dotted vertical lines were drawn at the optimal value by using 5-fold cross-validation and the 1-SE criteria. (b) Shows the coefficient profiles of 106 radiomics feature. The vertical dotted line was drawn at the value selected in (a). The Lambda value of 0.1638, with Log(Lambda) = -1.809 was chosen, and 2 nonzero coefficients were selected. (c) ROC curves for Rad-score-2-year in the test set composed by ninety lymph. (d, e) Lymph node local control curve with Rad-score-2-year (Kaplan-Meier). P values were < 0.001 and 0.025 in the training and the validation group respectively (long-rank).
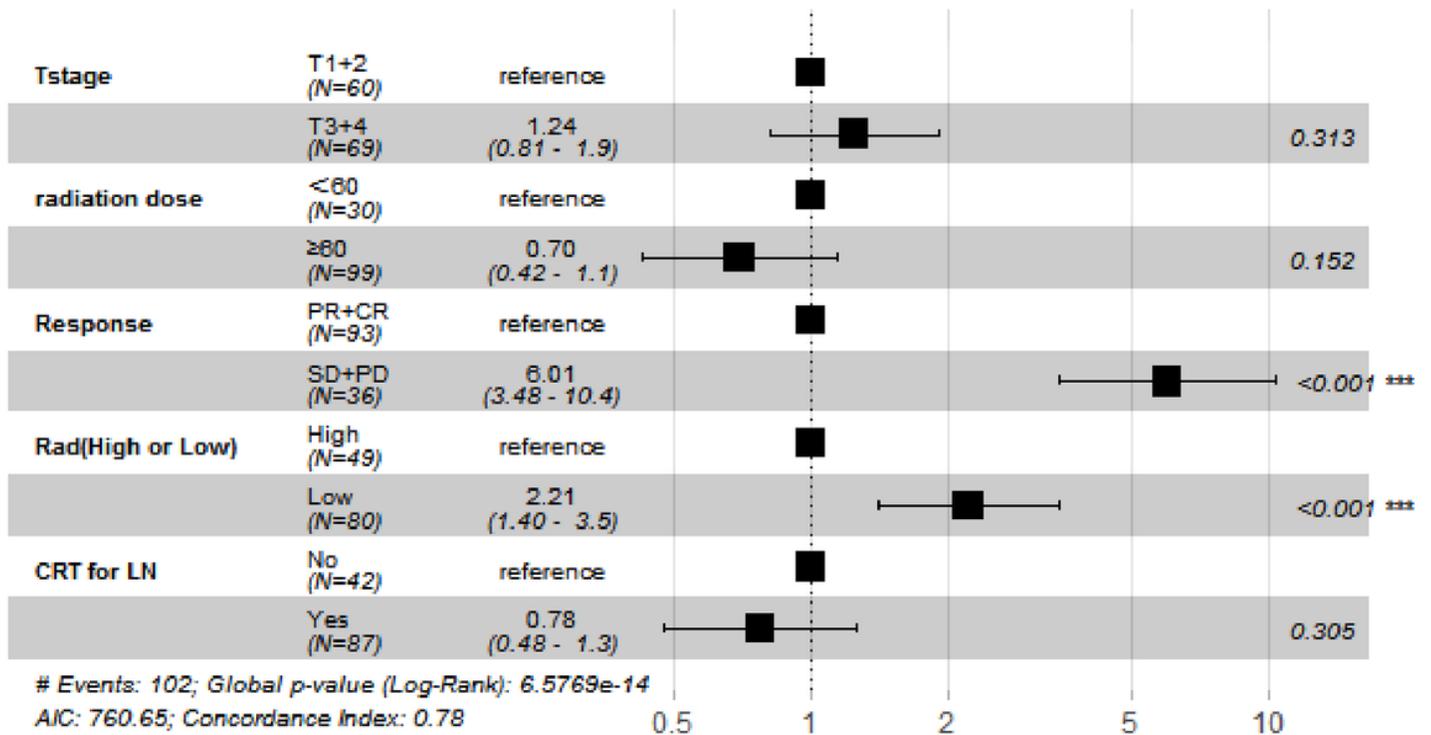
**Figure 3**

Cox regression analysis for 2-year local control. Unresponse(SD+PD) and low Rad-score were high-risk factors for local recurrence within 2 years after chemoradiotherapy.

## Supplementary Files

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