Clinical Radiology 86 (2025) 106906

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Delta-radiomics features combined with haematological index predict pathological complete response after neoadjuvant immunochemotherapy in resectable non-small cell lung cancer

D. Xiong [a,b,†], J. Li [c,†], L. Li [b], F. Xu [b], T. Hu [b], H. Zhu [b], X. Xu [d], Y. Sun [d], S. Yuan [a,b,c,*]

[a] *Department of Oncology, Affiliated Hospital of Southwest Medical University, Luzhou, China*
[b] *Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, China*
[c] *Department of Radiation Oncology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China*
[d] *Qingdao Municipal Hospital, Qingdao, Shandong, China*

ARTICLE INFORMATION

Article history:
Received 9 August 2024
Received in revised form
29 December 2024
Accepted 4 February 2025

AIM: This study aimed at assessing the value of enhanced computed tomography (CT)-based delta-radiomics features (Delta-RFs) and Delta-RFs combined with haematological dynamic changes in predicting pathological complete response (PCR) after neoadjuvant immunochemotherapy in non-small cell lung cancer (NSCLC).

MATERIALS AND METHODS: From January 2021 to August 2023, in total, 165 patients with stage IB–IIIB NSCLC (training, n=115, validation, n=50) who received neoadjuvant immunochemotherapy before surgery, were retrospectively enrolled. Radiomic features were extracted from tumour region of interest on pretreatment and pre-operation enhanced CT images. Delta-RFs are defined as the relative net change in radiomics features between pre-neoadjuvant immunochemotherapy and pre-operation stage. The least absolute shrinkage and selection operator was used to ensure optimal feature selection to calculate the radiomics score (Rad-score) for predicting PCR. Univariate and multivariate logistic regression analyses were performed to screen the factors related to PCR and predictive models were then constructed.

RESULTS: Forty percent patients showed PCR (66/165) after neoadjuvant immunochemotherapy. Nine Delta-RFs were selected as the most predictive factors for PCR. Logistic regression analysis showed that the Rad-score (OR = 8.542, 95% CI: 3.367–21.673, $P<0.001$) and ΔLMR (OR = 2.637, 95% CI: 1.094–6.359, $P=0.031$) were independent factors associated with PCR. With respect to predicting PCR, the Delta-RF model and the combined model both achieved satisfactory areas under the curve in the training (area under the curve [AUC]: 0.74, 0.788) and the validation was found to be cohort (AUC: 0.718, 0.737). The calibration curve

* Guarantor and correspondent: S. Yuan, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, 250117, China.
E-mail address: yuanshuanghu@sina.com (S. Yuan).
† Dali Xiong and Jiaran Li contribute equally to this work.

https://doi.org/10.1016/j.crad.2025.106906

showed that the predicted value of Delta-RF combined with haematological dynamic change model was in good agreement with the observed value. Decision curve analysis represented that the model exhibits high clinical practicability.

CONCLUSIONS: The Delta-RF model based on enhanced CT and the combined model can aid in efficient prediction of PCR after neoadjuvant immunochemotherapy in NSCLC, and the combined model can predict PCR performance better than Delta-RF model alone after neoadjuvant immunochemotherapy.

Abbreviations

Delta-RFs	delta-radiomics features
NSCLC	non-small cell lung cancer
LASSO	the Least Absolute Shrinkage and Selection Operator
Rad-score	radiomics score
PCR	pathological complete response
DCA	decision curve analysis
N-PCR	non-pathological complete response
ROI	region of interest
RFs	radiomics features
ICC	inter-class correlation coefficient
ROC	receiver operating characteristic
OR	odds ratio
CI	confidence interval
AUC	area under the curve
NLR	neutrophil-lymphocyte ratio
PLR	platelet-lymphocyte ratio
SII	systemic immune-inflammation index
LMR	lymphocyte-monocyte ratio
ANC	absolute neutrophil count
ALC	absolute lymphocyte count
CT	computed tomography
PET	positron emission tomography

Introduction

Lung cancer poses a significant global health challenge. It is the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases.[1] It brings forward a high risk of recurrence and death after radical resection of early-stage disease.[2–4] A meta-analysis was conducted by the NSCLC Meta-analysis Collaborative Group,[5] and it was reported that preoperative chemotherapy significantly improved the overall survival (OS) rate, time to distant recurrence, and recurrence-free survival in patients with resectable NSCLC. However, the absolute difference in 5-year recurrence-free survival and overall survival with neoadjuvant chemotherapy compared with surgery alone is only 5% to 6%, and the rate of pathological complete response (PCR) is very low (approximately 4%).[6] In the recent years, remarkable advancements have been made in the field of NSCLC immunotherapy. According to the literature, neoadjuvant immunochemotherapy significantly improves the rates of event-free survival and PCR of patients compared with neoadjuvant chemotherapy alone in resectable NSCLC.[7,8] Further, numerous studies are using PCR as a surrogate endpoint to predict survival benefits in neoadjuvant therapy clinical trials, and patients with a PCR exhibit significantly longer OS and progression-free survival than those with non-pathological complete response (N-PCR).[7] Thus, an alternative method for predicting response to neoadjuvant therapy is urgently required. Moreover, an accurate prediction of PCR can aid in the decision-making process to formulate correct treatment strategy in a timely manner. This avoids possible undertreatment or overtreatment and also prevents unnecessary complications associated with surgery. However, unfortunately, for resectable NSCLC, reliable marker for predicting PCR after neoadjuvant therapy is currently not available.

In cancer patients, the process of using imaging data (such as computed tomography [CT] and positron emission tomography [PET]) to determine tumour characteristics (such as lesion volume, shape, and texture description), thereby revealing associations with the diagnosis, prediction, and prognosis of tumours, is defined as radiomics.[9] In contrast to radiomics, which reflects static conditions, Delta-radiomics features (Delta-RFs) are changes in RFs, which provide a multi-temporal comparison that explores phenotypic changes in tissues or lesions occurring after treatment.[10] Some studies have reported that Delta-RFs have been successfully used in predicting patient response to chemotherapies for colorectal cancer liver metastases[11] and metastatic renal cell cancer[12] and in identifying patients with esophageal cancer, with the chances of developing radiation pneumonitis during treatment.[13] However, to date, studies on the use of Delta-RFs in predicting PCR after neoadjuvant immunochemotherapy in NSCLC have rarely been reported.

Accumulated literature evidences have shown the impact of the immune system and inflammatory factors on the proliferation, differentiation, and metastasis of cancer cells.[14] Further, immune checkpoint inhibitors can stimulate tumour antigen release and antigen-presenting cell function, thereby allowing immune cells to exert anti-tumour effects and improve patient prognosis.[15,16] Previous studies have shown that systemic immune–inflammation (SII) index can independently predict major pathologic response in patients treated with neoadjuvant immunotherapy.

Survival analysis has shown a significant correlation of high post-treatment neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and SII index with poor OS and event-free survival.[17] Moreover, the NLR and SII could predict a patient's response to immunotherapy and survival in various advanced solid tumours.[18–20] Noteworthily, the dynamic changes in peripheral blood immune cells can reflect the changes in the tumour microenvironment and capture anti-tumour immune responses, thus reflecting the clinical results of immune checkpoint inhibitors. However, few studies have used the relative changes in NLR, PLR, lymphocyte–monocyte ratio (LMR) and SII as indicators to determine the response of patients with NSCLC to neoadjuvant immunotherapy. Therefore, systematic exploration of the correlation between dynamic changes in peripheral blood biomarkers and PCR after neoadjuvant immunotherapy in NSCLC is also highly desirable.

In this study, the relative changes in Delta-RFs and NLR, PLR, LMR, and SII index were included to explore the value of Delta-radiomics in predicting PCR, as well as the performance of predicting PCR after combining haematological dynamic changes. This approach may provide more accurate treatment predictions for NSCLC patients and help physicians make individualised treatment decisions.

Materials and methods

Ethics statement

This study was approved by the ethical review board, and obtained waivers of informed consent from patients and their families. The workflow of this study is shown in Fig 1.

Study design and population

This retrospective study aimed at evaluating the ability of enhanced CT-based radiomics in predicting PCR, and it further determined whether the constructed RFs could serve as potential imaging markers for predicting PCR. The study included 165 patients with NSCLC who were treated with neoadjuvant immunochemotherapy between January 2021 and August 2023. The inclusion criteria are as follows: (1) age ≥ 18 years and good physical fitness status, (2) NSCLC diagnosed by histopathological analysis, (3) clinical stage IB–IIIB (AJCC 8th Edition), (4) surgery after neoadjuvant immunochemotherapy, and (5) complete enhanced CT imaging data before neoadjuvant immunochemotherapy and before surgery. The exclusion criteria are as follows: (1) neoadjuvant immunochemotherapy conducted for less than two cycles, (2) NSCLC concurrent with other cancer types, (3) tumour stage not between IB and IIIB, and (4) non-enhanced CT image or image not available. Patient clinicopathological information, including sex, age, smoking status, tumour site, histology, stage, PCR or N-PCR status, haematology data, and details concerning neoadjuvant treatment, such as agents and course of treatment, were collected from the electronic database. Pathological response was assessed by pathologists specialised in NSCLC, and PCR was defined as the presence of nonviable cancer cells in all the resected specimens. Patients were randomly divided into the training and validation cohorts (7:3). The neoadjuvant immunochemotherapy regimen for all patients included paclitaxel and platinum combined with PD-1/PD-L1 monoclonal antibody, such as tislelizumab, nivolumab,

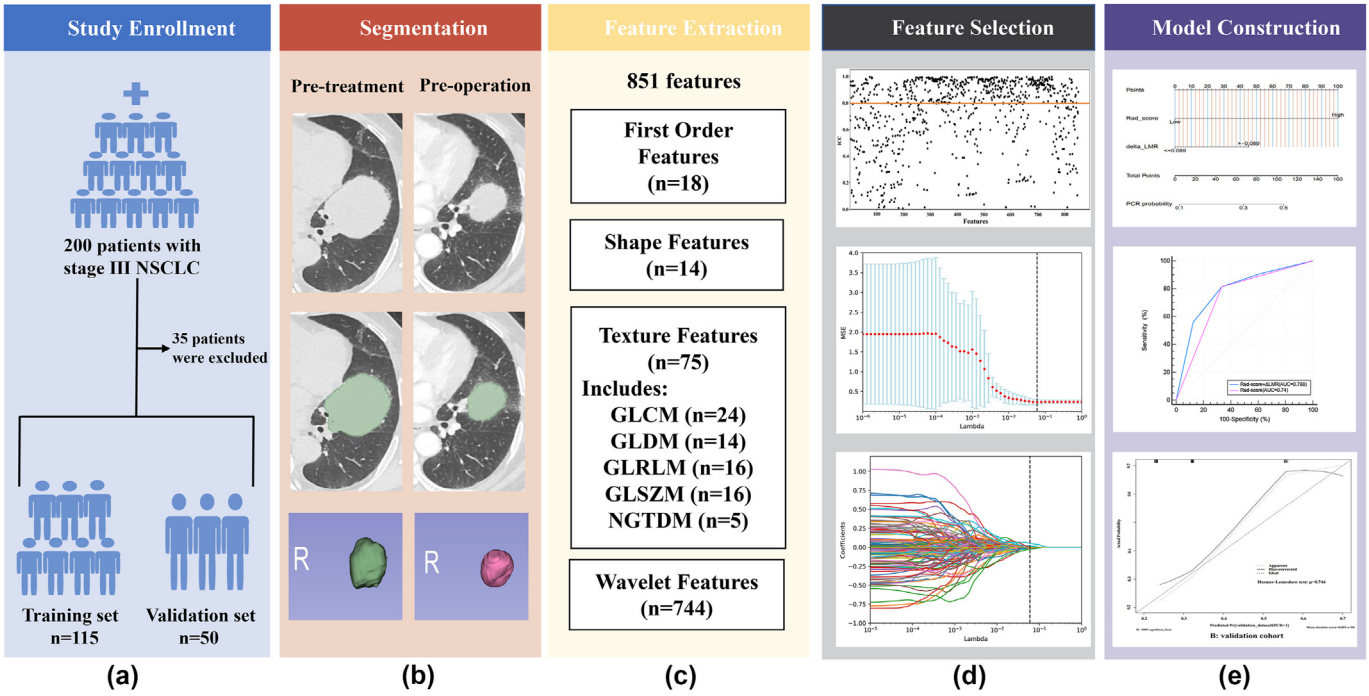

Figure 1 Workflow of the study.

sintilimab, camrelizumab, durvalumab, toripalimab, penpulimab, and atezolizumab.

CT image acquisition and tumour segmentation

Enhanced CT images before neoadjuvant immunochemotherapy and before surgery were obtained for all patients. DICOM format-enhanced CT images with a thickness of 5 mm were obtained from the Picture Archiving and Communication System for analysis. Enhanced CT images were imported into a three-dimensional (3D) slicer (a medical image processing and navigation software, version5.2.2, http://www.slicer.org,usa), and a physician with 5 years of experience in reading chest CT images manually sketched the tissue layer by layer with the tumour as the region of interest (ROI) on pre-neoadjuvant therapy and pre-operation-enhanced CT images. The ROI was reviewed by two experienced clinicians.

Radiomics feature extraction

The Pyradiomics package of the 3D slicer software was used to extract high-throughput radiomics features from the ROI of CT images obtained for each patient. In all, 851 RFs were extracted from each ROI, including original features and small filter features. The original feature included shape feature, first order statistic feature, and texture feature. Further, texture features included GLSZM, NGTDM, GLCM, GLRLM, and GLDM. Small filter features included wavelet-LLL, wavelet-LLH, wavelet-LHL, wavelet-LHH, wavelet-HLL, wavelet-HLH, wavelet-HHL, and wavelet-HHH (Fig 1c).

Delta-RF selection and radiomics score construction

RFs before neoadjuvant immunotherapy and before surgery were separately extracted for Delta-RF calculation. The Delta-RF is defined as the relative net change of RF between two time points as follows:[21]

$$\text{Relative Net Change} = (\text{Feature}_{\text{pre-operation}} - \text{Feature}_{\text{pretreatment}}) / \text{Feature}_{\text{pretreatment}}$$

To reduce operator bias and extract stable RFs, two months after the completion of the first sketch, the CT images of 30 randomly selected patients were re-sketched by another physician. Based on the results of the two RF extractions, the inter-class correlation coefficient (ICC) was calculated herein. Stable and reproducible Delta-RFs with ICC $\geq$ 0.8 were included in the analysis. The least absolute shrinkage and selection operator (LASSO), which is suitable for high-dimensional data, was used to select the most useful predictive features. The radiomics score (Rad-score) was calculated for each patient via the linear combination of selected features weighted by their respective coefficients.

Analysis of peripheral blood laboratory data

The progression of tumour is closely related to inflammation.[22,23] Neutrophils, lymphocytes, and platelets can reflect the inflammation and immune status of the body to a certain extent, and LMR, NLR, PLR, and SII index as inflammatory complex indicators have also been proven to be important factors in predicting the prognosis of lung cancer.[24–26] The absolute neutrophil counts (ANCs), absolute lymphocyte counts (ALCs), absolute platelet counts, and absolute monocyte counts of patients before undergoing neoadjuvant therapy and pre-operation were recorded. In case of multiple blood tests, the data closest to the time of treatment and surgery were selected. NLR was calculated as the ratio of ANC to ALC; PLR as the ratio of platelet count to ALC; LMR as the ratio of ALC to monocyte counts; and SII index as the absolute platelet count multiplied by NLR. Moreover, the relative changes in NLR, PLR, LMR, and SII index were calculated by subtracting the pretreatment value from the pre-operation value and then dividing by the pretreatment value. This relative change was represented as ΔNLR, ΔPLR, ΔLMR, and ΔSII, respectively.

Construction of the prediction model

The receiver operating characteristic (ROC) curve of Rad-score was drawn to predict PCR. The value corresponding to the point on the curve with the largest Youden index (Youden index = sensitivity + specificity−1) was selected as the best truncation value of Rad-score. Further, patients were divided into high and low Rad-score groups according to the best truncation value of Rad-score. Haematological indices were also divided into high and low groups following the same method. In the training cohort, the independent factors related to PCR were selected by univariate and multivariate logistic regression analyses. Based on the results of multivariate analysis, a visualisation nomogram prediction model of Delta-RF combined with haematological indices was established. The prediction ability of the model was verified in the validation cohort. In the training cohort, DeLong test was employed for comparative analysis of the statistical differences in area under the curve (AUC) between nomogram model and Delta-RF model. The ROC curve was used to evaluate the performance of each model, and the validation was conducted in the validation cohorts. The alignment curve derived by the Hosmer–Lemeshow test was used to evaluate the agreement between the predicted and the actual observed values. Decision curve analysis (DCA) was carried out to evaluate the clinical effectiveness.

Statistical analysis

In this study, patients were randomly divided into training and validation cohorts (7:3). The former was used for developing machine learning models, while the latter was used for validating and evaluating the performance of machine learning models. All statistical analyses in this study were conducted by using the SPSS 25.0 statistical software. The χ^2 test or Fisher's exact test was used to evaluate the balance of clinical features between the training and validation cohorts. The best cutoff values of Rad-score, age, and haematological indices were

determined by the point with the largest Jordan index on the ROC curve. The LASSO was implemented by using "Python" (version V3.9). Univariate and multivariate logistic regression analyses were conducted to screen for factors associated with PCR. Medcalc (version V20.022) was used to plot the ROC curve and calculate the AUC for evaluating the predictive performance of the model. Finally, the DeLong test was used to compare ROC curves. All tests in this study were bilateral, and P values < 0.05 were considered statistically significant.

Results

Baseline characteristics

In all, 165 patients were included in the study. All patients received 2–4 cycles of neoadjuvant immunochemotherapy before surgery. The pathological specimens were evaluated by an experienced pathologist and reviewed by a thoracic surgeon. Among the 165 patients, 66 (40%) achieved PCR, 43 were in the training cohort, and 23 in the validation cohort. Supplemenatry Table S1 presents the details about the patients. There was no significant difference in baseline characteristics between the two cohorts ($P>0.05$).

Delta-RF selection and Rad-score construction

In total, 851 features were extracted from the enhanced CT images before neoadjuvant therapy and before surgery for each patient, respectively. After sketching the ROI twice, Delta-RFs with ICC < 0.8 were excluded. Finally, 470 Delta-RFs were included as stable features in the subsequent analysis. In the training cohort, to ensure the data comparability, the Delta-RFs were standardised by using Z-score. To reduce the redundancy and avoid unnecessary complex and cumbersome calculations and modelling, LASSO was used to reduce the feature dimension and the optimal penalty coefficient λ ($\lambda_{min} = 0.0599$) was adjusted by the 10-fold cross-validation method. Finally, nine Delta-RFs, with the most predictive capability for PCR, were selected (Fig 1d). These included two shape features, one texture feature, and six small filter features. The corresponding Delta-RFs and weight coefficients are shown in Supplemenatry Table S2. The selected Delta-RFs and their corresponding weight coefficients were linearly combined to calculate the Rad-score for each patient in the validation cohort. The formula for calculating Rad-score is shown in Supplemenatry Table S3.

Construction of the prediction model

In the training cohort, the best cutoff value for Rad-score was 0.3607 and that for ΔLMR was −0.089. Univariate analysis results (Table 1) showed that Rad-score (odds ratio [OR], 8.75; 95% confidence interval [CI], 3.518–21.761; $P<0.001$) and ΔLMR (OR, 2.768; 95% CI: 1.263–6.064; $P=0.011$) were correlated with PCR. The two above-mentioned factors were included in multivariate analysis, and the results showed that Rad-score (OR, 8.542; 95% CI:

Table 1
Results of univariate and multivariate analyses in the training cohort.

Variables		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Gender	Male	1			
	Female	1.005 (0.228–4.432)	0.995		
Age	≥49.5	1			
	<49.5	3.134 (0.354–27.766)	0.305		
Smoking status	Never	1			
	Former/current	0.868 (0.350–2.153)	0.761		
Tumour location	Left lung	1			
	Right lung	1.216 (0.570–2.591)	0.613		
Histology	SCC	1	0.188		
	ADC	0.383 (0.130–1.125)	0.081		
	Others	0.459 (0.046–4.594)	0.508		
Clinical stage	IB	1	0.857		
	IIA	0.250 (0.513–3.387)	0.442		
	IIB	0.467 (0.767–13.353)	0.608		
	IIIA	0.625 (0.037–10.449)	0.744		
	IIIB	0.750 (0.041–13.677)	0.846		
Δ NLR	Low	1			
	High	2.118 (0.749–5.987)	0.157		
Δ PLR	Low	1			
	High	1.233 (0.426–3.568)	0.699		
Δ LMR	Low	1			
	High	2.768 (1.263–6.064)	0.011	2.637 (1.094–6.359)	0.031
Δ SII	Wild	1			
	High	2.625 (0.421–16.378)	0.302		
Rad-score	Low	1			
	High	8.75 (3.518–21.761)	<0.001	8.542 (3.367–21.673)	<0.001

Abbreviations: ADC, adenocarcinoma; CI, confidence interval; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PLR , platelet–lymphocyte ratio; OR, odds ratio; Rad-score, radiomics score; SCC, squamous cell carcinoma; SII, systemic immune–inflammation.

3.367−21.673; $P<0.001$) and ΔLMR (OR, 2.637; 95%CI: 1.094−6.359; P=0.031) were the independent influencing factors for PCR. First, herein, a Delta-RF model (AUC = 0.74, 95% CI: 0.647−0.834) was constructed in the training cohort. Subsequently, based on the results of the multivariate analysis, Delta-RF and ΔLMR were combined to develop the visual nomogram model (AUC = 0.788, 95% CI: 0.700−0.876) (Fig 2). Typical images of PCR and N-PCR and corresponding risk factors are shown in Fig 3. The nomogram model exhibited a higher AUC than the Delta-RF model (DeLong test, $P=0.03$) (Fig 4a). Next, consistent results were obtained in the validation cohort, wherein the predictive efficacy of the nomogram model outperformed that of the Delta-RF model (AUC 0.737 vs. 0.718, DeLong test, $P=0.5698$) (Fig 4b). Finally, the consistency between the prediction of PCR by using the nomogram model and actual observations was confirmed using calibration curves. Moreover, the Hosmer−Lemeshow test results indicated the absence of any statistical difference between the predictive and actual values in the training cohort ($P=0.597$) (Fig 5a). Consistent results were also observed in the validation cohort ($P=0.744$) (Fig 5b). Consequently, the nomogram model shows good agreement between the predicted probability and the actual observations with respect to PCR ($P>0.05$). The decision curve shows that nomogram model exhibits high clinical practicability (Supplementary Figure S1).

Discussion

This study aimed at evaluating the predictive value of the enhanced CT-based Delta-RF model and Delta-RF combined with haematological dynamic changes model (nomogram model) for PCR after neoadjuvant immunochemotherapy in NSCLC. The results showed that both models have high AUC values; i.e., 0.74 and 0.788 in the training cohort, and 0.718 and 0.737 in the validation cohort. Both models showed good predictive ability for PCR after neoadjuvant immunochemotherapy; however, the nomogram model exhibited better predictive performance than the Delta-RF model. The nomogram model was validated by DCA, which demonstrated the good clinical utility of the model.

PCR is being used by an increasing number of researchers as a surrogate endpoint for predicting survival benefits of neoadjuvant therapy in clinical trials.[7] A recent study[27] revealed that achievement of PCR is associated with significantly improved long-term prognosis in patients undergoing neoadjuvant immunochemotherapy. Therefore, accurate prediction of PCR after neoadjuvant immunochemotherapy for NSCLC is crucial. Prediction of PCR before surgery for NSCLC neoadjuvant immunochemotherapy can improve the criterion for selection of specific treatment strategies for patients, provide patients with important information, help them select the most suitable course of treatment, and potentially avoid unnecessary surgery. However, there is no consensus on predicting PCR after neoadjuvant immunotherapy in patients with NSCLC. Radiomics, as an emerging image analysis technology, is capable of extracting high-throughput information on tumour heterogeneity from medical images.[28] In the recent years, the role of radiomics in the management of cancer patients has been extensively investigated. Moreover, radiomics has been successfully used to predict lung cancer phenotypes, find out the efficacy of immunotherapy, identify the radiation pneumonitis, and identify subtypes of

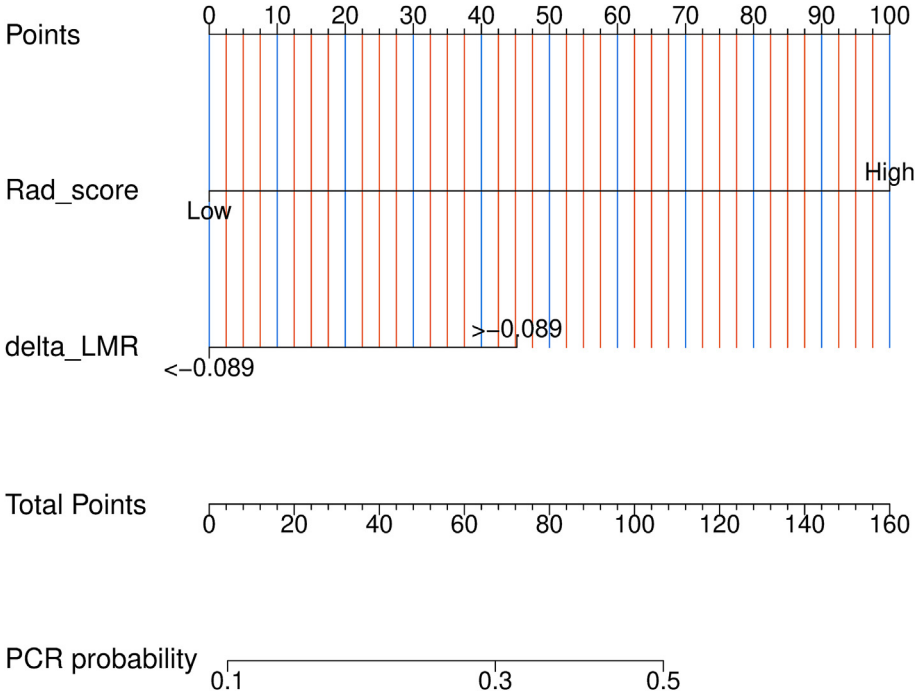

Figure 2 Nomogram incorporating Rad-score, and delta-LMR to predict PCR. delta-LMR: delta lymphocyte-monocyte ratio; PCR: pathological complete response; Rad-score: radiomics score.

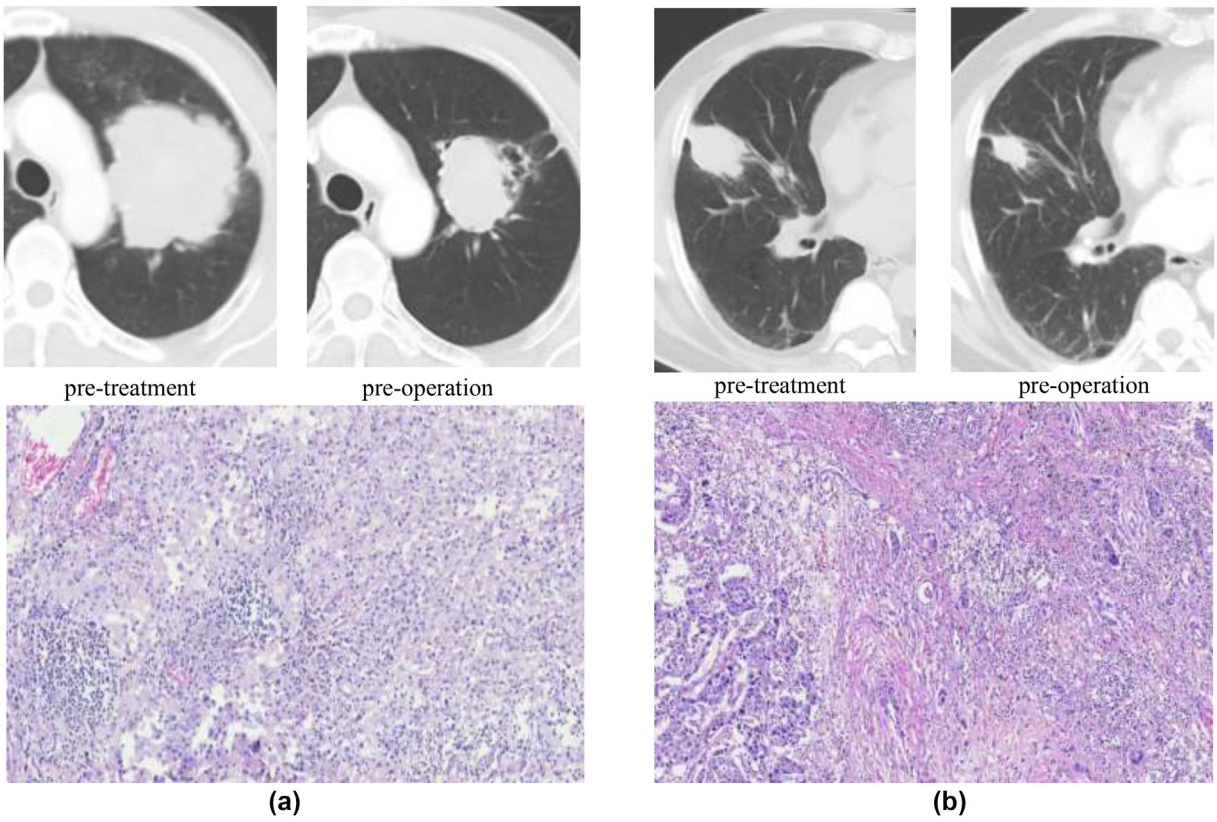

Figure 3 Representative images of patients with PCR and N-PCR. (a) PCR in a patient with a high Rad-score and high delta-LMR. (b) N-PCR in a patient with a low Rad-score and low delta-LMR. delta-LMR, delta lymphocyte-monocyte ratio; PCR, pathological complete response; Rad-score, radiomics score.

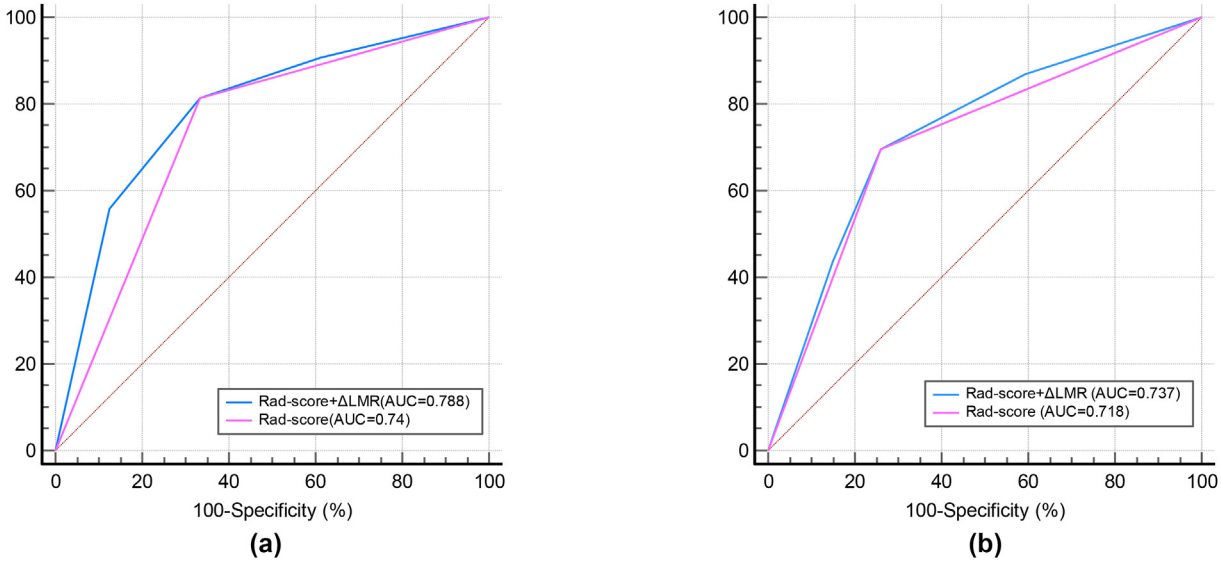

Figure 4 Predictive performance evaluation of each model for predicting PCR. The nomogram model shows superior prediction ability compared wtih Delta-RF model in training cohort (AUC: 0.788 vs 0.74) and validation cohort (AUC: 0.737 vs 0.718), respectively. AUC, area under the curve; Delta-RF: delta-radiomics feature; PCR, pathological complete response; Vs, versus; .

pulmonary nodules, etc.[10,29–31] Notably, radiomics has also been used to predict pathological responses to neoadjuvant therapy in cancer patients. Study has shown that Delta-RFs exhibit good predictive accuracy for PCR in esophageal squamous cell carcinoma patients receiving neoadjuvant chemoradiotherapy.[32] Similarly, Han *et al.*[33] retrospectively analysed a model constructed based on CT Delta-RFs to predict the major pathological responses of NSCLC towards

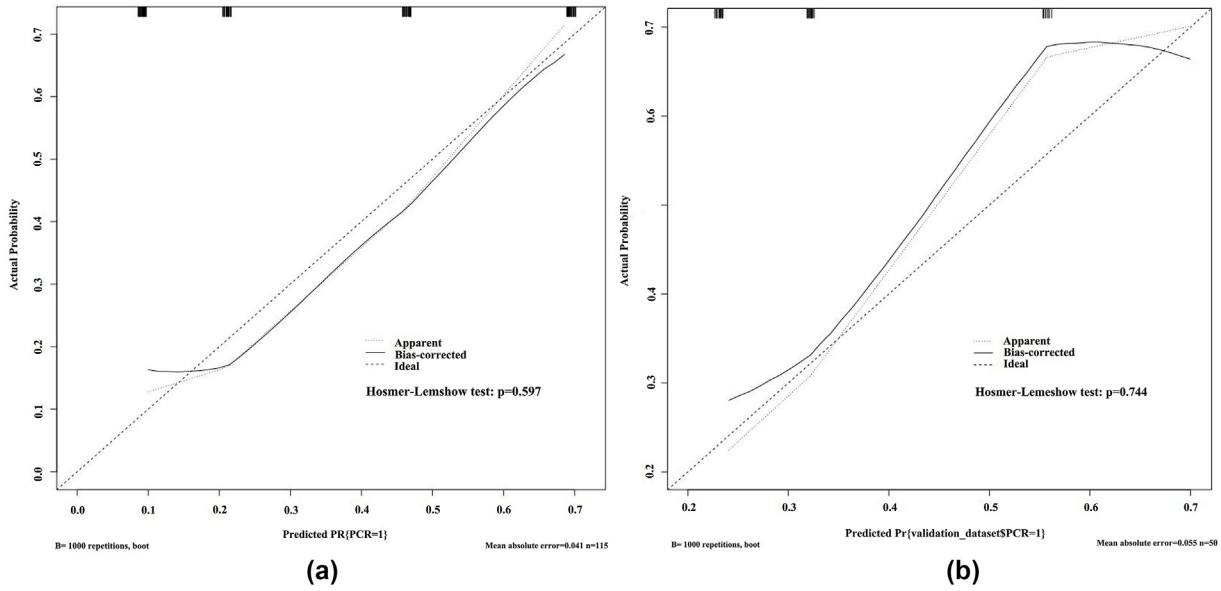

Figure 5 Calibration curve of the nomogram model in training cohort (a) and validation cohort (b). The x-axis represents the predicted PCR, and the y-axis represents the actual PCR. Calibration curve of the nomogram model is presented as a solid line. The black diagonal dashed line indicates the ideal nomogram. The more solid line is close to the diagonal dashed line, the more agreement there is between the predicted results and the actual condition. PCR, pathological complete response.

neoadjuvant immunochemotherapy, and achieved satisfactory AUC values of 0.768, 0.732, 0.833, and 0.716 in the training, test, and two external validation databases, respectively. Given the current research gap in the field of Delta-RFs to predict PCR, this study explored the performance of CT-based Delta-RFs and Delta-RFs combined with haematological dynamic changes in predicting PCR after neoadjuvant immunochemotherapy in NSCLC patients. The results showed that the nomogram model constructed in this study exhibited good performance for predicting PCR after neoadjuvant immunochemotherapy in patients with NSCLC and it could be used as an important decision-making tool for identifying PCR after neoadjuvant immunotherapy.

Single-time-phase RFs have limited representation of changes within tumours before and after immunochemotherapy. Moreover, Delta-RFs, which can assess the relative net change in RFs in longitudinal images, provide a wealth of information to identify, quantify, and potentially predict changes over the course of treatment.[34] According to a literature study, the Delta-RF model outperforms the pre-treatment radiomics model in predicting major pathological response after neoadjuvant immunochemotherapy for NSCLC.[33] Cunliffe *et al.* evaluated the use of pre-/post-radiotherapy changes in CT texture features for identifying patients with esophageal cancer with radiation pneumonitis, and the fusion of multiple dynamic indicators was found to be more valuable in predicting the onset and severity of radiation pneumonitis than a single point-in-time indicator.[13] Therefore, Delta-RF modelling was adopted in this study. The results showed that the AUC of the Delta-RF model established herein was 0.74/0.718 in the training cohort/validation cohort, which also indicated that Delta-RFs had a good predictive performance for PCR after immunochemotherapy in NSCLC patients.

With the rapid development of immunotherapy, static peripheral blood predictive biomarkers based on treated tissues have been unable to accurately predict the anti-tumour immune response in neoadjuvant immunotherapy patients. Therefore, identification of more convenient and dynamic biomarkers for predicting PCR rates and survival in patients undergoing neoadjuvant immunotherapy is urgently required. In this study, the correlation between dynamic changes in haematological indices and PCR was also evaluated, and it was found that ΔLMR, a derivative index of LMR, was strongly correlated with PCR (P=0.011). The index was calculated by using ALC and absolute monocyte count. Both monocytes and neutrophils can be differentiated from granulocyte—mononuclear progenitor cells, which exhibit a similar effect on inflammation development. Monocytes can produce a variety of inflammatory mediators, such as vascular endothelial growth factor, epidermal growth factor, and tumour necrosis factor, through macrophages, thereby promoting tumour cell growth and angiogenesis.[35] These in turn affect the prognosis of tumour patients. Therefore, based on the changes in imaging features and ΔLMR before and after immunochemotherapy, in this study, a predictive model was constructed and it was validated in a validation cohort. Fortunately, the nomogram model with the addition of ΔLMR indicator showed an AUC of 0.788 in the training cohort, which significantly improved the predictive efficacy of the Delta-RF model. The nomogram model also showed a good predictive performance in the validation cohort (AUC = 0.737). However, the AUC values in the training and validation cohort differed significantly possibly because of population heterogeneity. Further, an

increase in predictive performance is not ideal, which may be related to the fact that ΔLMR is a dynamic index affected by several factors, such as bacterial infection. Undeniably, a lot more systematic explorations are further demanded to address the limitations of the present model and conduct further multi-omics, large-scale studies to promote the use of multi-omics fusion in the management of lung cancer patients, which will be pursued in the future.

To reduce the redundancy and complexity of calculation and modelling, this study performed feature reduction and screening through LASSO and 10-fold cross-validation, and finally selected Delta-RF to be the most predictive for PCR. However, there are thousands of quantitative RFs in images, and to obtain more stable and reliable predictive features, deep learning models have attracted significant research attention for its practical application in medical image processing due to its superior performance in language and image recognition. Interestingly, deep learning models have also shown satisfactory performance in predicting the main pathological response to neoadjuvant immunochemotherapy in NSCLC patients. For instance, Lin *et al.*[36] retrospectively analysed clinical and imaging data of 62 NSCLC patients receiving neoadjuvant immunochemotherapy. They extracted radiomics features and deep learning features from lung cancer lesions and constructed an integrated model combining clinical features, radiomics features, and deep learning features for accurate efficacy prediction. Li *et al.*[37] explored the performance of different machine learning models for PCR prediction and found that the machine learning model based on Delta-RFs performed better than those based on single time-stage post-immunochemotherapy RFs. In the future, this study can also be continued to obtain more stable and reliable prediction features through deep learning, establish the best model, and improve the prediction efficiency, to help clinicians accurately predict PCR.

In the era of precision tumour therapy, development of personalised diagnosis and treatment plans according to the heterogeneity of patients has become a research hotspot. The accurate prediction of PCR can provide important reference value for the follow-up treatment of tumour patients. For example, according to the viewpoint of many oncologists, a significant number of patients who theoretically achieve PCR may simply need to undergo segmentectomy or radiation therapy as an alternative to lobectomy or total pneumonectomy.[38,39] Furthermore, it has also been shown that patients with PCR for rectal cancer who wait for observation have comparable outcomes with surgery.[40] In other words, many patients with a high predicted probability of achieving PCR could avoid adjuvant or surgical treatment, thereby leading to the reduction in drug toxicities or surgical complications and saving treatment costs. By contrast, if clinicians can predict in advance that the probability of obtaining PCR after neoadjuvant immunochemotherapy is low, the intensity of treatment for patients can be increased or the treatment mode can be changed timely, which can save a life. The visualisation of the nomogram developed in this study simplifies the prediction process, which enhances the feasibility of its convenient application in clinical practice. Accurate prediction of PCR in NSCLC contributes significantly to therapeutic decisions and is expected to improve clinical outcomes in NSCLC patients in the near future.

However, there are some limitations of this study. First, the ROI of the tumours was manually delineated by experienced physicians, including all lesions with clear boundaries and some lesions with unclear boundaries or difficult to distinguish tumour regions. Although ICC was introduced in this study to reduce subjective delineation bias to a certain extent, it still cannot be ruled out that it may have some impact on the model stability. Thus, development of more accurate ROI determination methods can be anticipated in future studies. Second, the small sample size and single-centre study design may lead to selection bias. Moreover, in this study, the relationship between Delta-RFs and prognosis was not explored due to the short duration of patient follow-up. In the future studies, multicentre, large-sample prospective studies should be conducted, with long-term follow-up of patients, to obtain increasingly reliable evidence and meaningful conclusions.

Conclusion

Our study shows that enhanced CT-based Delta-RF model and nomogram model can predict PCR after neoadjuvant immunotherapy for NSCLC. The nomogram model can predict PCR better than the Delta-RF model. Our nomogram model has the potential to personalise neoadjuvant immunotherapy for patients with NSCLC.

Author contribution

1. Guarantor of integrity of the entire study: S. Yuan, D. Xiong.
2. Study concepts and design: D. Xiong, J. Li, L. Li, S. Yuan
3. Literature research; Clinical studies; Manuscript preparation: D. Xiong, J. Li.
4. Experimental studies / data analysis: D. Xiong, J. Li, F. Xu, X. Xu, Y. Sun, H. Zhu.
5. Statistical analysis: D. Xiong, J. Li, T. Hu.
6. Manuscript editing: D. Xiong, J. Li, L. Li, F. Xu, T. Hu, H. Zhu, X. Xu, Y. Sun, S. Yuan.

Ethics

This study was approved by the ethical review board of the Shandong Cancer Hospital and Institute (ethics approval number: SDTHEC2024004014) and obtained waivers of informed consent from patients and their families.

Funding

This study was supported in part by the National Natural Science Foundation of China (NSFC82073345), Natural Science Innovation and Development Joint Foundation of

Shandong Province (ZR202209010002), Jinan Clinical Medicine Science and Technology Innovation Plan (202019060) and the Taishan Scholars Program to Shuanghu Yuan.

Conflict of interest

The authors declare no conflict of interest.

Data availability

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

Consent for publication

Not applicable.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2025.106906.

References

1. Langer CJ, Besse B, Gualberto A, *et al*. The evolving role of histology in the management of advanced non-small-cell lung cancer. *J Clin Oncol* 2010;**28**:5311–20. https://doi.org/10.1200/JCO.2010.28.8126.
2. Al-Kattan K. Disease recurrence after resection for stage I lung cancer. *Eur J Cardio-Thoracic Surg* 1997;**12**:380–4. https://doi.org/10.1016/S1010-7940(97)00198-X.
3. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. *The Lancet* 2000;**355**:479–85. https://doi.org/10.1016/S0140-6736(00)82038-3.
4. Carnio S, Novello S, Papotti M, *et al*. Prognostic and predictive biomarkers in early stage non-small cell lung cancer: tumor based approaches including gene signatures. *Transl Lung Cancer Res* 2013;**2**:372–81. https://doi.org/10.3978/j.issn.2218-6751.2013.10.05.
5. Group NM analysis C. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet (London, England)* 2014;**383**:1561. https://doi.org/10.1016/S0140-6736(13)62159-5.
6. Hellmann MD, Chaft JE, William WN, *et al*. Pathologic response after neoadjuvant chemotherapy in resectable non-small cell lung cancers: proposal for the use of "major pathologic response" as a surrogate endpoint. *Lancet Oncol* 2014;**15**:e42–50. https://doi.org/10.1016/S1470-2045(13)70334-6.
7. Ren S, Xu A, Lin Y, *et al*. A narrative review of primary research endpoints of neoadjuvant therapy for lung cancer: past, present and future. *Transl Lung Cancer Res* 2021;**10**:3264–75. https://doi.org/10.21037/tlcr-21-259.
8. Provencio M, Nadal E, Insa A, *et al*. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2020;**21**:1413–22. https://doi.org/10.1016/S1470-2045(20)30453-8.
9. Sollini M, Cozzi L, Antunovic L, *et al*. PET Radiomics in NSCLC: state of the art and a proposal for harmonization of methodology. *Sci Rep* 2017;**7**:358. https://doi.org/10.1038/s41598-017-00426-y.
10. Cousin F, Louis T, Dheur S, *et al*. Radiomics and delta-radiomics signatures to predict response and survival in patients with non-small-cell lung cancer treated with immune checkpoint inhibitors. *Cancers (Basel)* 2023;**15**:1968. https://doi.org/10.3390/cancers15071968.
11. Rao SX, Lambregts DM, Schnerr RS, *et al*. CT texture analysis in colorectal liver metastases: a better way than size and volume measurements to assess response to chemotherapy? *United Eur Gastroenterol J* 2016;**4**:257. https://doi.org/10.1177/2050640615601603.
12. Goh V, Ganeshan B, Nathan P, *et al*. Assessment of response to Tyrosine Kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. *Gastrointestinal Imaging* 2011;**261**.
13. Cunliffe A, Armato SG, Castillo R, *et al*. Lung texture in serial thoracic computed tomography scans: correlation of radiomics-based features with radiation therapy dose and radiation pneumonitis development. *Int J Radiat Oncol Biol Phys* 2015;**91**:1048–56. https://doi.org/10.1016/j.ijrobp.2014.11.030.
14. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. *Nat Rev Clin Oncol* 2015;**12**:584–96. https://doi.org/10.1038/nrclinonc.2015.105.
15. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature* 2011;**480**:480–9. https://doi.org/10.1038/nature10673.
16. Smyth MJ, Ngiow SF, Ribas A, *et al*. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nat Rev Clin Oncol* 2016;**13**:143–58. https://doi.org/10.1038/nrclinonc.2015.209.
17. Huai Q, Luo C, Song P, *et al*. Peripheral blood inflammatory biomarkers dynamics reflect treatment response and predict prognosis in non-small cell lung cancer patients with neoadjuvant immunotherapy. *Cancer Sci* 2023;**114**:4484–98. https://doi.org/10.1111/cas.15964.
18. Fornarini G, Rebuzzi SE, Banna GL, *et al*. Immune-inflammatory biomarkers as prognostic factors for immunotherapy in pretreated advanced urinary tract cancer patients: an analysis of the Italian SAUL cohort. *ESMO Open* 2021;**6**:100118, https://doi.org/10.1016/j.esmoop.2021.100118.
19. Nenclares P, Gunn L, Soliman H, *et al*. On-treatment immune prognostic score for patients with relapsed and/or metastatic head and neck squamous cell carcinoma treated with immunotherapy. *J Immunother Cancer* 2021;**9**:e002718, https://doi.org/10.1136/jitc-2021-002718.
20. Valero C, Lee M, Hoen D, *et al*. Pretreatment neutrophil-to-lymphocyte ratio and mutational burden as biomarkers of tumor response to immune checkpoint inhibitors. *Nat Commun* 2021;**12**:729. https://doi.org/10.1038/s41467-021-20935-9.
21. Fave X, Zhang L, Yang J, *et al*. Delta-radiomics features for the prediction of patient outcomes in non–small cell lung cancer. *Sci Rep* 2017;**7**:588. https://doi.org/10.1038/s41598-017-00665-z.
22. Proctor MJ, Morrison DS, Talwar D, *et al*. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. *Eur J Cancer* 2011;**47**:2633–41. https://doi.org/10.1016/j.ejca.2011.03.028.
23. Ji H, Niu X, Yin L, *et al*. Ratio of immune response to tumor burden predicts survival via regulating functions of lymphocytes and monocytes in diffuse large B-cell lymphoma. *Cell Physiol Biochem* 2018;**45**:951–61. https://doi.org/10.1159/000487288.
24. Hu B, Yang XR, Xu Y, *et al*. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res* 2014;**20**:6212–22. https://doi.org/10.1158/1078-0432.CCR-14-0442.
25. Shi Z, Zheng D, Tang X, Du Y. Correlation of immune inflammatory indices and nutritional risk index with prognosis in patients with non-small cell lung cancer.
26. Liu J, Li S, Zhang S, *et al*. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. *J Clin Lab Anal* 2019;**33**:e22964, https://doi.org/10.1002/jcla.22964.
27. Yang Z, Wang S, Yang H, *et al*. Treatment patterns and clinical outcomes of patients with resectable non–small cell lung cancer receiving neoadjuvant immunochemotherapy: a large-scale, multicenter, real-world study (NeoR-World). *J Thorac Cardiovasc Surg* 2024;**168**:1245–1258.e17. https://doi.org/10.1016/j.jtcvs.2024.02.006.
28. Lambin P, Rios-Velazquez E, Leijenaar R, *et al*. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012;**48**:441–6. https://doi.org/10.1016/j.ejca.2011.11.036.
29. Beig N, Khorrami M, Alilou M, *et al*. Perinodular and intranodular radiomic features on lung CT images distinguish adenocarcinomas from granulomas. *Radiology* 2018;**290**:783. https://doi.org/10.1148/radiol.2018180910.

30. Cheng J, Pan Y, Huang W, *et al*. Differentiation between immune checkpoint inhibitor-related and radiation pneumonitis in lung cancer by CT radiomics and machine learning. *Med Phys* 2022;**49**:1547. https://doi.org/10.1002/mp.15451.
31. Thawani R, McLane M, Beig N, *et al*. Radiomics and radiogenomics in lung cancer: a review for the clinician. *Lung Cancer* 2018;**115**:34–41. https://doi.org/10.1016/j.lungcan.2017.10.015.
32. Fan L, Yang Z, Chang M, *et al*. CT-based delta-radiomics nomogram to predict pathological complete response after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma patients. *J Transl Med* 2024;**22**:579. https://doi.org/10.1186/s12967-024-05392-4.
33. Han X, Wang M, Zheng Y, *et al*. Delta-radiomics features for predicting the major pathological response to neoadjuvant chemoimmunotherapy in non-small cell lung cancer. *Eur Radiol* 2023;**22**, https://doi.org/10.1007/s00330-023-10241-x. Published online September.
34. Nasief H, Zheng C, Schott D, *et al*. A machine learning based delta-radiomics process for early prediction of treatment response of pancreatic cancer. *npj Precis Onc* 2019;**3**:25. https://doi.org/10.1038/s41698-019-0096-z.
35. Diaz-Montero CM, Finke J, Montero AJ. Myeloid derived suppressor cells in cancer: therapeutic, predictive, and prognostic implications. *Semin Oncol* 2014;**41**:174. https://doi.org/10.1053/j.seminoncol.2014.02.003.
36. Lin Q, Wu HJ, Song QS, *et al*. CT-based radiomics in predicting pathological response in non-small cell lung cancer patients receiving neoadjuvant immunotherapy. *Front Oncol* 2022;**12**:937277, https://doi.org/10.3389/fonc.2022.937277.
37. Li K, Li Y, Wang Z, *et al*. Delta-radiomics based on CT predicts pathologic complete response in ESCC treated with neoadjuvant immunochemotherapy and surgery. *Front Oncol* 2023;**13**:1131883, https://doi.org/10.3389/fonc.2023.1131883.
38. Kanzaki R, Ose N, Funaki S, *et al*. The outcomes of induction chemoradiotherapy followed by surgery for clinical T3-4 non-small cell lung cancer. *Technol Cancer Res Treat* 2019;**18**, https://doi.org/10.1177/1533033819871327. 1533033819871327.
39. Montagne F, Guisier F, Venissac N, *et al*. The role of surgery in lung cancer treatment: present indications and future perspectives—state of the art. *Cancers* 2021;**13**:3711. https://doi.org/10.3390/cancers13153711.
40. Habr-Gama A, Julião GPS, Vailati BB, *et al*. Management of the complete clinical response. *Clin Colon Rectal Surg* 2017;**30**:387. https://doi.org/10.1055/s-0037-1606116.