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Artificial Intelligence in Health

REVIEW ARTICLE

Prognostic evaluation using radiomics after stereotactic body radiotherapy in early-stage lung cancer

Melek Yakar*

Department of Radiation Oncology, Faculty of Medicine, Osmangazi University, Eskişehir, Turkey

Abstract

Non-small cell lung cancer (NSCLC), the leading cause of cancer-related deaths, is the most common subtype of lung cancer with an incidence of 85%. Stereotactic body radiotherapy (SBRT) is a curative treatment option for patients with early-stage NSCLC who cannot undergo surgery due to medical reasons or who refuse surgery. Radiomics non-invasively extracts advanced imaging features invisible to the human eye from medical images. Radiomics has prognostic value in predicting oncological outcomes after lung SBRT. Although studies on this subject are available in the literature, they are quite heterogeneous. There is a need for large-scale multicenter studies in which standard imaging techniques are used to obtain radiomic features, artificial intelligence-based segmentations are used to eliminate differences between contours, and SBRT dose schemes with appropriate therapeutic indexes are applied. This review aimed to interpret the existing studies and emphasize the clinical importance of radiomics, which can contribute to personalized treatment. A comprehensive literature search was conducted through the PubMed database using a wide range of keywords, which yielded 11 peer-reviewed articles published between 2017 and 2024. Seven articles evaluated computed tomography radiomics, and four evaluated fluorodeoxyglucose positron emission tomography-computed tomography radiomics. Oncological outcomes are not always identical in patients with a similar history receiving similar treatments at the same stage and age. Clinical, demographic, or treatment-related data are insufficient to predict prognosis and determine personalized treatment. Incorporating radiomics to these data can help establish models with higher accuracy and achieve personalized treatment.

Keywords: Artificial intelligence; Lung cancer; Stereotactic body radiotherapy; Prognosis; Radiomics

***Corresponding author:**
Melek Yakar
(myakar@ogu.edu.tr)

Citation: Yakar M. Prognostic evaluation using radiomics after stereotactic body radiotherapy in early-stage lung cancer. *Artif Intell Health*. 2024;1(4):1-11. doi: 10.36922/aih.3541

Received: April 30, 2024

Accepted: August 1, 2024

Published Online: October 16, 2024

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1. Introduction

Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer with an incidence of 85% and has the highest cancer-related mortality. Stereotactic body radiotherapy (SBRT) is a curative treatment option for patients with early-stage NSCLC who cannot undergo surgery due to medical reasons or who refuse surgery. Although 92 – 98% of local tumor control can be achieved using SBRT in these patients, varying recurrence patterns have been reported in 18 – 20% of the patients.[1] Stereotactic irradiation focuses multiple X-rays at different angles on a small localized lesion, provided

that good immobilization is achieved. The most important difference between SBRT and conventional fractionation is that high doses are delivered to the target volume in several fractions, resulting in a high biological effective dose (BED). Li *et al*. reported a statistically significant difference in 3- and 5-year local control between the SBRT arm and conventional fractionated radiotherapy with SBRT arm.[2]

Recent advances in science and technology have revealed that each tumor, even within the same type of cancer, has several varying phenotypic and genotypic characteristics. This inhomogeneity between tumors leads to different oncological responses to standard treatments administered at the same cancer stage.[3] Identifying the factors associated with relapse is important to initiate salvage treatment for patients as soon as possible. Underdosing may be a reason for tumor recurrence after SBRT. Therefore, predicting tumor response before treatment can help in adjusting dose prescription to prevent relapses.

Radiomics quantitatively describes the characteristics of medical images. It calculates features and provides numerical values using mathematical formulas. Radiomics features are based on the distribution of pixels and voxels in the region of interest (ROI) and the relationship between them. Radiomics provides pixel and voxel characteristics of images that are indistinguishable to the human eye.[4] Personalized treatment involves treatment tailored to each patient according to tumor characteristics, with the aim of improving oncological outcomes and obtaining a good therapeutic index while reducing side effects. The principle of personalized treatment is based on determining the heterogeneous structure of the tumor and its characteristic features and elucidating the treatment option accordingly.[5]

Radiomics has prognostic value in predicting oncological outcomes after lung SBRT. However, prediction models have been created using parameters such as radiomics, dosimetrics, and patient and treatment characteristics to evaluate local tumor control, recurrence, and tumor-related survival in patients with lung cancer receiving SBRT.

This review aimed to summarize the role of radiomics features obtained from different imaging methods in predicting the prognosis of patients receiving lung SBRT. Moreover, it emphasizes the clinical importance of radiomics and its ability to contribute to personalized treatment by interpreting existing studies.

2. Material and methods

2.1. Search strategy and study selection

A comprehensive literature search was conducted in the PubMed database using a wide range of keywords, including "Lung cancer," "SBRT," "radiomics," "computed tomography," "FDG PET-CT," "prognosis," "prediction of response to treatment," "survival," "local control," and "recurrence."

This review included studies evaluating quantitative features extracted from baseline or follow-up computed tomography (CT) or positron emission tomography (PET)-CT scans against treatment response in patients treated with SBRT for NSCLC of any stage or lung metastases. Studies whose full texts were available were included. The exclusion criteria were (1) studies that did not evaluate radiological response as an end point, (2) studies focusing entirely on methodological aspects of radiomics, (3) studies using phantoms or animal models, and (4) studies without original data, such as reviews and editorials. In total, 11 peer-reviewed articles published during 2017 – 2024 were included, of which seven articles evaluated CT radiomics, and four articles evaluated fluorodeoxyglucose (FDG) PET-CT radiomics.

3. Prognosis evaluation using radiomics

According to studies in the literature, CT and even more frequently planning CTs for radiotherapy are generally used to extract radiomics features, and PET-CT is used less frequently. In some studies, clinical and dosimetric features were also added to the models established using radiomics features.

The effect of radiomics features obtained from different imaging methods on prognostication has not been explored comparatively. Some studies have reported the varying impact of different imaging techniques and estimation algorithms on radiomics features.[6-8] There is no standard imaging, scanning parameter, algorithm, or radiomics feature. Data from existing studies and subsequent multicenter randomized studies are required for standardization.

3.1. CT-based radiomics models

CT and rarely magnetic resonance imaging are used during radiotherapy planning, and extensive patient data are accumulated during the standard treatment planning process. Radiomics features obtained from CT are used to predict oncological outcomes such as evaluating treatment response and predicting prognosis and recurrence patterns. Although planning CT is frequently used because CT is currently performed at the treatment planning stage, some studies use diagnostic thorax CT acquired at the diagnosis stage or during follow-up.

Hyunh *et al*. evaluated 112 patients diagnosed with early-stage lung cancer who received SBRT using both static-free breathing (FB) CT and respiratory-gated CT (average intensity projection [AIP]). The median SBRT

BED was 151.2 (range: 100 – 151.2) Gy. Radiomics features of all patients were obtained using both FB CT and AIP CT. A total of 644 radiomics features were obtained using the MATLAB 2013 toolbox. Both FB CT and AIP CT yielded 19 significant radiomics features, with six features (two features of tumor shape, three features of intensity histogram or statistics of the tumor, and one feature of homogeneity of the tumor tissue) being similar in both image sets and the remaining 13 being completely different from each other but similar to each image type in both image sets. The unique radiomics features of FB CT images were statistical ($n = 6$) and textural ($n = 7$) features. Of the 13 unique radiomics features of AIP CT images, there were eight textural, four statistical, and one shape feature. The median follow-up duration was 20.8 months. Distant metastasis (DM) developed in 20.5% of the patients ($n = 23$), and the average time to metastasis was 10.0 months. Locoregional recurrence (LRR) developed in 21.4% of the patients ($n = 24$), and the median time until LRR developed was 8.8 months. The 2-year estimates for LRR and DM were 70.9% and 74.0%, respectively. The concordance index (CI) was used to evaluate prognostic performance. We found that FB CT radiomics features were unrelated to DM development, whereas AIP CT radiomics features describing tumor shape and heterogeneity were compatible with DM development (CI: 0.638 ± 0.676). No imaging radiomics features were associated with LRR in their study. Compared with FB CT images, AIP CT images contained more valuable information regarding disease recurrence in patients with early-stage NSCLC receiving SBRT. According to their study, AIP CT images may be a valuable non-invasive technique to predict recurrence.[9]

Kakino *et al*. conducted a local and distant recurrence prediction study using breath-hold CT-based radiomics features in 573 patients with early-stage NSCLC who received SBRT. The patients were categorized into two groups: 464 patients (from 10 centers) were evaluated as the training group and 109 patients (from 1 center) were evaluated as the test group. Important variables were determined using the adaptive least absolute shrinkage and selection operator (LASSO) method. Three prognostic models (clinical, radiomics, and combined) were trained using the random survival forest (RSF) algorithm. The CI values in the clinical, radiomics, and combined models constructed using clinical and radiomics features were 0.57, 0.55, and 0.61 for LRR and 0.59, 0.67, and 0.68 for DM, respectively. According to their study, although DM could be predicted through the RSF algorithm in patients with early-stage NSCLC who received SBRT using breath-hold CT-based radiomics features, the same algorithm was considered to have a lower potential to predict LRR.[10]

Sawayangi *et al*. randomly divided 358 patients treated with SBRT into training (250 patients) and validation (108 patients) groups and estimated the overall survival (OS) using both clinical variables and CT-based radiomics features. They applied 42 – 64 Gy SBRT in 4 – 10 fractions (BED10 range: 75 – 166 Gy). To extract radiomics features, the gross tumor volume (GTV) was contoured in the expiratory phase of the planning CT. Radiomics features categorized as gray level size region matrix features calculated from GTV in the pretreatment CT image had high accuracy for OS prediction in patients with early-stage NSCLC treated with curative SBRT. These findings indicate that the operating system predicted from multiple linear regression analysis is similar to the actual operating system. These data may be important in selecting patients who would benefit from increasing treatment intensity, such as increasing the radiotherapy dose or using different fractionations and adding other treatments such as chemotherapy/immunotherapy/targeted therapies.[11]

Luo *et al*. evaluated 119 patients and 129 lesions treated with SBRT with a median of 48 Gy (range: 18 – 70 Gy) in a median of four fractions (range: 1 – 12). Like other studies, they created clinical, radiomics, and combined models. They generated radiomics features based on planning CT. Of 1502 radiomics features, four were identified as important variables using the LASSO method. Logistic regression (LR), decision tree, and support vector machine (SVM) algorithms were used to create the optimal model for evaluating local tumor control. LR was determined as the prediction algorithm with the highest accuracy rate, with the accuracy rates of the radiomics, clinical, and combined models being 67.4%, 82.0%, and 85.4% in the training group and 92.9%, 77.5%, and 82.5% in the validation group, respectively. The combined model performed statistically significantly better than the radiomics ($P = 0.025$) and clinical ($P = 0.033$) models in the training group, whereas both radiomics and clinical models showed similar performance ($P = 0.613$). According to their study, the combined model based on radiomics features and clinical and dosimetric parameters can be used to predict 1-year local tumor control in patients with lung cancer receiving SBRT.[12]

Isoyama-Shirakawa *et al*. conducted a study on 125 patients with early-stage NSCLC treated with SBRT. They generated the radiomics score and investigated the effect of this score in predicting LC and metastasis-free survival (MFS). The median BED10 for SBRT was 88.9 (range: 61.2 – 119.0) Gy. Planning CT-based radiomics features were generated. From 432 radiomics features, five important variables were identified using the LASSO method. The radiomics score was obtained using five significant radiomics features, which was statistically

significantly associated with both LC (>0.043 vs. ≤0.043, $P = 0.042$) and MFS (>0.304 vs. ≤0.304, $P < 0.001$). Considering clinical factors, their study suggested that tumor histology, tumor diameter, and radiomics score are vital factors in predicting NSCLC recurrence patterns after SBRT.[13]

Lafata *et al.* evaluated the FB planning CT-based radiomics features of 70 patients with early-stage NSCLC who received SBRT with a mean of 51 Gy at Duke University. Only two of 43 radiomics features, namely, Homogeneity2 and Long-Run-High-Gray-Level-Emphasis, were considered significant variables and were associated with LC. The area under the curve (AUC) values of the multivariable LR prediction models for recurrence, local recurrence, and non-local recurrence were 0.72 ± 0.04, 0.83 ± 0.03, and 0.60 ± 0.04, respectively. These data suggest that relatively dense tumors with homogeneous rough tissue are associated with higher rates of local recurrence. This was supported by both univariate and multivariate analyses that showed that CT-based radiomics features may be associated with local recurrences after SBRT in patients with Stage 1 NSCLC.[14]

Unlike other studies, Li *et al.* evaluated radiomics features in follow-up CT after SBRT. In their study, a dose of 50 Gy was administered in five fractions to 54 patients with early-stage NSCLC, 48 Gy was administered in four fractions to three patients, and 60 Gy was administered in eight or five fractions to two patients. The first control CT was taken 1 – 3 months after the completion of SBRT (median 91 days, range: 33 – 112 days) and used to extract radiomics features. As imaging features, 34 manually determined radiological features (semantics) describing the lesion, lung, and thorax, and 219 quantitative imaging features (radiomics) for the lesion were extracted. Cox proportional hazards models and Harrell's C index were used to predict OS, relapse-free survival (RFS), and locoregional RFS (LR-RFS), and a five-fold cross-validation was performed for the prognostic model. Data from a median follow-up of 42 months were available. Eastern Cooperative Oncology for OS model Group performance status, vascular involvement, lymphadenopathy, and radiomics features considered important were included in the study. Vascular involvement, pleural retraction, lymphadenopathy, vessel attachment, and relative enhancement were included in the RFS model. In the LR-RFS model, vascular involvement, lymphadenopathy, circularity, and radiomics features were included in the study. The AUC, which was used to evaluate the performance of the models, was >0.8 for all models. According to their study, the disease progression can be predicted even 3 months after SBRT using the model established using CT imaging features, which might be helpful in clinical decision-making.[15] The abovementioned studies are summarized in Table 1.

The field of radiomics, which quantitatively analyzes extensive data obtained from medical images, has significant potential for predicting treatment outcomes. Nevertheless, a standardized imaging method has not yet been developed. Moreover, the segmentation of the target region for the collected data varies among researchers. Studies have been conducted using several varying radiomics features using different software, and no consensus has been achieved on this issue. Multicenter radiomics-based prediction algorithms with higher accuracy can be generated using a standard imaging method and artificial intelligence (AI)-based segmentation.

3.2. PET- and CT-based radiomics models

FDG PET-CT is a molecular imaging technique that combines metabolic and functional assessments, improving the diagnostic accuracy and initial staging and restaging of lung cancer and influencing treatment optimization and monitoring of treatment response. Although most studies on PET-CT have shown that the standardized uptake value can be used as a prognostic indicator of OS, some studies do not support this.[16,17]

Evaluation of tumor heterogeneity is gaining importance due to radiomics features obtained from different imaging modalities. If prognosis can be predicted accurately before treatment through radiomics, the most beneficial personalized treatment can be administered to patients. Prognostic prediction studies have been conducted using a combination of radiomics and more classical PET parameters, and current prognostic prediction studies are conducted using both PET and CT radiomics features to create models with higher accuracy.[18,19]

Dissaux *et al.* conducted a prognostic prediction study using 18F-FDG PET-CT radiomics features in patients with early-stage lung cancer receiving SBRT. They included 64 patients from three different centers in the training set and 23 patients from one center in the test set. The primary tumor was segmented semiautomatically using the fuzzy locally adaptive Bayesian algorithm on PET images and manually on low-dose CT images. ComBat was used to harmonize the radiomics features obtained from the four institutions, yielding 184 (92 PET and 92 CT) radiomics features. In the training set, significant variables in the univariate analysis were added to the multivariate regression model. Models were constructed by combining the obtained independent prognostic factors. Two important variables were each obtained from PET and CT. The median follow-up duration was 21.1 (range: 1.7 – 63.4) and 25.5 (range: 7.7 – 57.8) months in

Table 1. SBRT response prediction studies using CT-based radiomics

Study and year	Imaging method used	Number of patients	Number of radiomics features and radiomics extraction method	Number of significant radiomics features	Important radiomics identification method	Algorithm/statistical method used	Oncological outcomes
Huynh *et al*., 2017[9]	FB CT and AIP CT	112	644, MATLAB 2013 toolbox	19	PCA and factor analysis (FactoMineR package)	Univariate and multivariate analyses	Seven AIP radiomics features were associated with DM (CI: 0.638±0.676)
Li *et al*., 2017[15]	Follow-up thorax CT after SBRT	59	219, Definiens Developer	166	Pearson's correlation	LR	LR model AUC (CI): OS: 0.88 (0.78 – 0.97) RFS: 0.86 (0.76 – 0.96) LR-RFS: 0.85 (0.74 – 0.95)
Lafata *et al*., 2019[14]	FB planning CT	70	43, MATLAB	2	SVD, LASSO	Multivariable LR models	AUC values of 0.72±0.04, 0.83±0.03, and 0.60±0.04, for recurrence, local recurrence, and non-local recurrence, respectively
Kakino *et al*., 2020[10]	Breath-hold planning CT	573	944, PyRadiomics Ver. 2.2.0	16	Adaptive LASSO	RSF	CI values for LR in clinical, radiomics, and combined models were 0.57 (0.39 – 0.75), 0.55 (0.38 – 0.73), and 0.61 (0.43 – 0.78), respectively Corresponding value for DM 0.59 (0.54 – 0.79), 0.67 (0.54 – 0.79), and 0.68 (0.55 – 0.81)
Luo *et al*., 2022[12]	FB planning CT	119	1502, PyRadiomics	4	LASSO	LR, DT, SVM	Best result for 1-year LC prediction in the combined model with LR AUC of 0.911 (training) and 0.818 (validation)
Sawayanagi *et al*., 2022[11]	FB planning CT	358	107, PyRadiomics v3.0.1	4 (OS) 2 (LRFS) 3 (PFS)	Regression model	Multiple linear regression	One radiomics factor remained a significant prognostic factor of overall survival (OS) (P=0.044)
Isoyama-Shirakawa *et al*., 2023[13]	FB planning CT	125	432, MATLAB-based Radiomics tools package	5	LASSO	Kaplan–Meier analysis and log-rank test	Radiomics score was significantly associated with MFS (P<0.001) and LC (P=0.042)

Abbreviations: FB: Free breathing; AIP: Average intensity projection; PCA: Principal component analysis; DM: Distant metastasis; CI: Concordance index; LASSO: Least absolute shrinkage and selection operator; RSF: Random survival forest; OS: Overall survival; LRFS: Local relapse-free survival; PFS: Progression-free survival; LR: Logistic regression; DT: Decision tree; SVM: Support vector machine; LC: Local control; MFS: Metastasis-free survival; SVD: Singular value decomposition; LR-RFS: Locoregional recurrence-free survival.

the training and test sets, respectively. No clinical variable was predictive of local tumor control in the univariate analysis. Similarly, two PET radiomics features and two CT radiomics features did not significantly predict local tumor control. The best predictive models in the training set were obtained by combining one feature from PET with one feature from CT, achieving 100% sensitivity and 96% specificity. Another model combining two PET features achieved 100% sensitivity and 88% specificity. The second model achieved an accuracy of 0.91 (sensitivity, 100%; specificity, 81%) in the test set. According to their study, two radiomics features derived from 18F-FDG PET were independently associated with local tumor control in patients with NSCLC receiving SBRT and can be combined into an accurate predictive model. This model can provide information regarding local tumor recurrence and assist in clinical decision-making.[20]

Oikonomou *et al*. evaluated the recurrence prediction algorithm using both PET-CT radiomics features and maximum standardized uptake value (SUVmax) values. Their study included 150 patients and 172 tumors, and 42 features were obtained from CT and PET. There were 11 important variables in the prediction models. OS, disease-specific survival, and regional control were estimated in the model established using radiomics features; however, neither SUVmax nor DFS could be predicted using radiomics models.[21]

In another study, 60% of 464 patients with early-stage lung cancer who received SBRT were included in the training set, 40% were included in the test set, and 63 patients from another center were included in the external test set. The SBRT dose was 40 – 60 Gy administered in 3 – 5 fractions. Differences between images from the two centers were eliminated using the ComBat harmonization method. A total of 318 radiomics features (106 from each imaging) were obtained from PET, PET-CT, and planning CT using the PyRadiomics toolbox. In the training and test sets, the C-statistics value for predicting regional and/or distant recurrences using the clinical model was 0.53 – 0.59 (95% CI: 0.41 – 0.67), that using the radiomics model was 0.70 – 0.78 (95% CI: 0.63 – 0.88), and that using the combined model was 0.50 – 0.62 (95% CI: 0.37 – 0.69), indicating that the radiomics model showed the best prediction performance. According to this study, radiomics features obtained from FDG PET-CT before SBRT performed better than clinical parameters in predicting regional and/or distant recurrence and determining adjuvant systemic therapy for patients with early-stage NSCLC.[22]

Similarly, Nemoto *et al*. conducted a recurrence prediction study using radiomics features from PET and CT images. They applied SBRT to 82 patients with NSCLC at 48 Gy/4 Fr, 50 Gy/4 Fr, or 55 Gy/4 Fr for T1 tumors and 60 Gy/10 Fr or 70 Gy/10 Fr for T2 tumors. They extracted 111 radiomics features using PyRadiomics from both planning CT and PET images. Using three different methods (chi-square test, minimum redundancy maximum relevance, and ReliefF), they obtained 42 important variables and created a model using four different algorithms (random forest, SVM, K-nearest neighborhood, and naive Bayes). SVM with PET radiomics (mean AUC: 0.646), naive Bayes with PET radiomics (mean AUC: 0.611), and SVM with CT radiomics (mean AUC: 0.645) exhibited the highest performance for local recurrence, regional lymph node metastasis, and DM. Their study demonstrated that the model combining PET imaging features and SVM may be useful for predicting local and regional lymph node recurrence and the model combining CT imaging features and SVM may be useful for predicting distant recurrence.[23]

4. Can radiomics be used in clinical practice?

Radiomics can be considered a signature of tumors. With gradual advancements in technologies in the field of medicine, personalized treatments are becoming important. Oncological outcomes are not always similar in patients at the same stage and age, with the same performance score, and receiving the same treatment. Radiomics is gaining importance in this regard. Tumor features that are not visible to the clinician can be revealed through radiomics and play a key role in determining the most accurate personalized treatment. Various medical imaging technologies, which are non-invasive methods, are used for staging patients with lung cancer for treatment selection. Evaluation of medical images is not completely objective and may vary between clinicians depending on the person's experience. Some radiomics features in medical images are not visible to the human eye. As summarized earlier, studies suggest that radiomics can be used as a non-invasive adjunct tool for personalized treatment selection and prediction of oncological response. Nevertheless, several technical difficulties, especially in feature engineering and statistical modeling, and the use of different methods limit a standardized approach; hence, the clinical use of radiomics still remains under development.

A standard contouring should be performed for the tumor or tumor microenvironment where radiomics features are planned to be studied. Determining the correct radiomics features may be difficult because of differences between users. Therefore, users must be experienced in this field and follow accepted guidelines. A well-trained AI segmentation system will also help in standardization. Furthermore, if the radiation oncologist and radiologist work

together on segmentation, the accuracy of segmentation can be increased.

Differences between centers in terms of obtaining imaging studies should be eliminated. Several parameters require standardization, such as the device used for imaging, use of contrast in CT, slice thicknesses, and the time between nuclear material injection and imaging.

Extraction of features involves a comprehensive quantification of tumor phenotypes. After image acquisition, preprocessing, and segmentation, radiomics features are extracted from two-dimensional (2D) or 3D ROIs in the images. A standard method for selecting ROIs is also lacking. For metastatic diseases, there is still no clear consensus on whether the metastatic focus or the primary focus should be segmented. Moreover, only the tumor and tumor microenvironment, which is usually created at a 5-mm margin to the tumor, can be used as ROIs for feature extraction. Furthermore, there is no consensus on whether radiomics features should be obtained from the original image or filtered images.[24]

There are different types of radiomics features, such as shape, first-order, and textural features. As it remains unclear which feature should be used at which stage of tumor, most studies investigate all radiomics features. There is also no consensus on whether 2D or 3D features should be used. The 2D radiomics features have been reported to be superior in some studies, whereas 3D features are reportedly superior in other studies in terms of prognosis.[25,26]

Due to the lack of knowledge on which type of radiomics features should be used in which tumors, hundreds of radiomics features are extracted; however, if all of them are used to create a model, it will generate an excessive number of features, causing confusion and overfitting of the data and decreasing the actual accuracy. It is important to consider that the extracted radiomics features may be related to each other, and feature selection should be conducted before modeling. It is also necessary to use radiomics feature selection methods that identify the most important features and remove redundant ones. As a standardized method for determining important variables has not yet been developed, different methods are used in various studies.[27]

After determining the important variables among 100 of radiomics features using appropriate methods, an accurate model is established. Researchers use different machine learning algorithms to create models. Each study has reported different algorithms with the best accuracy. This leads to further confusion among clinicians. Thus, the most effective algorithm for determining prognosis remains unclear.

Furthermore, data must be distributed evenly, which otherwise would increase the risk of overfitting. Radiomics studies are still ongoing at the clinical trial level, and there exist several parameters that require standardization. In this regard, clinicians and engineers must standardize these parameters through a joint investigation. Standardization of parameters is essential for the use of radiomics in routine clinical practice; otherwise, each study may identify different radiomics features as important variables, resulting in varying accuracy rates of different algorithms in multiple studies. Considering this heterogeneity, it would be inappropriate to use radiomics as a standard in routine clinical practice.

As technology advances, the importance of data also increases. Performing tumor and organ-at-risk segmentation in the radiotherapy planning stage is a routine procedure for radiation oncologists and is included in the treatment planning of each patient. From this perspective, algorithms need to be trained on a large amount of processed data in radiation oncology clinics. These valuable data should not be ignored and must be considered to contribute significantly to standardization.

In summary, radiomics is a promising non-invasive method for prognostic prediction and post-treatment follow-up, wherein medical images can be analyzed. It has the potential to facilitate personalized treatment selection with low cost and high sensitivity. If the appropriate personalized treatments are administered, patients can avoid unnecessary treatment and high treatment-related costs. Radiomics can be used as an important biomarker in treatment decisions, prognosis determination, and follow-up after accurate standardization.

5. Delta radiomics

Radiomics has been developed to evaluate feature changes at different time points, an approach often referred to as "delta radiomics." This method is used to examine the effects of feature changes after certain steps in the patient's workflow (for instance, after a certain treatment).[28-30] Delta radiomics is a promising field of research and allows changing and modulating the treatment approach due to its predictive power.[31]

The vast majority of radiomics methods used in existing studies depend on imaging data obtained at a single time point, often imaging tumors before the start of treatment. Delta radiomics reveals the changes in feature values during treatment by extracting quantitative features from image sets obtained throughout the treatment process.[32,33] Delta radiomics may improve cancer diagnosis, prognosis, patient follow-up, or evaluation of treatment response.[34,35] Some studies have shown that delta radiomics is effective

in investigating immunotherapy response or predicting relapse in oncological patients.[36-38]

Delta radiomics has been used and found to be useful in evaluating the response to chemotherapies in colorectal cancer, liver metastases, and metastatic renal cell cancer.[39,40] Delta radiomics has also been used to predict the risk of developing radiation pneumonitis during treatment in patients with esophageal cancer.[41] Delta radiomics features obtained from PET-CT images have been used to estimate prognosis in patients with NSCLC.[32]

Changes in the tumor during treatment can be detected using delta radiomics, which can thus help modify treatment strategies. For instance, in a patient planned for neoadjuvant radiotherapy, radioresistant tumors can be detected using delta radiomics, and the patient can be referred to surgery earlier. When unresponsive patients for lung SBRT are detected during this process, they can be protected from unnecessary treatment toxicities. Hence, standardizing the stages of obtaining delta radiomics can both contribute to personalized treatments and protect patients from unnecessary treatment toxicities.

6. AI and ethical issues in cancer treatment

Ethical issues surrounding AI in healthcare concern privacy, bias, and discrimination, as well as whether it can replace human judgment. Where there is technology, there is always the risk of inaccuracy and data breach. Moreover, wrong decisions can result in undesirable and devastating consequences in the treatment of patients with cancer. There is no clear regulation on legal and ethical issues regarding the role played by AI in healthcare; therefore, this issue needs careful consideration.

Innovations and new developments in technology accelerate scientific progress. It is important to explore strategies to eliminate the potentially disastrous problems of AI technologies.

Machine learning algorithms are effective in identifying and analyzing or classifying large amounts of data, referred to as "Big Data." Big Data are used to train algorithms. Using more data to train an algorithm generally increases the accuracy rate of the algorithm. The machine requires a set of rules and instructions, generally written in the form of algorithms, to perform tasks. Nevertheless, when newly acquired data are used, the machine gradually gains the ability to become more flexible and operate in different situations accordingly. This situation may increase the demand for data and sometimes cause sharing of personal or public information without considering user privacy. Ethics and moral values vary across countries and even regions within countries. Ethnic groups and nations have different norms. When defining values from humans to machines, ethical rules such as deontology and virtue found in humans should also be considered for using machines.

Our current moral systems are derived fundamentally from our responsibilities to other people. Therefore, a non-human system, *that is*, AI, cannot be expected to understand existing moral systems.[42] These issues must be resolved before using AI in human-related decisions.

AI systems should be data stewards. Only the required data may be used and then deleted, which is also defined as "data minimization." Data should be encrypted and used only by authorized individuals. Data must be collected, used, and shared according to privacy and personal data laws. Before using patient data, patients' consent must be obtained, and Ethics Committee permission should also be obtained from the concerned authorities.[43]

7. Conclusion

SBRT is considered the first treatment option with similar oncological outcomes in patients with early-stage NSCLC who cannot undergo surgery or refuse surgery for medical reasons.

It is important to determine the patient's risk of recurrence during the treatment planning stage to determine the most ideal personalized treatment. If patients with a high risk of recurrence can be selected in advance, the treatment intensity can be increased by changing the radiotherapy dose or schedule.

Acknowledgments

None.

Funding

None.

Conflict of interest

The author declares having no competing interests.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Chang JY, Mehran RJ, Feng L, *et al*. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): Long-term results of a single-arm, prospective trial with prespecified comparison to surgery. *Lancet Oncol*. 2021;22(10):1448-1457.

   doi: 10.1016/S1470-2045(21)00401-0

2. Li C, Wang L, Wu Q, *et al*. A meta-analysis comparing stereotactic body radiotherapy vs conventional radiotherapy in inoperable stage I non-small cell lung cancer. *Medicine* (*Baltimore*). 2020;99(34):e21715.

   doi: 10.1097/MD.0000000000021715

3. Jameson JL, Longo DL. Precision medicine--personalized, problematic, and promising. *N Engl J Med*. 2015;372(23):2229-2234.

   doi: 10.1056/NEJMsb1503104

4. Bertolini M, Trojani V, Botti A, *et al*. Novel harmonization method for multi-centric radiomic studies in non-small cell lung cancer. *Curr Oncol*. 2022;29(8):5179-5194.

   doi: 10.3390/curroncol29080410

5. 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(4):441-446.

   doi: 10.1016/j.ejca.2011.11.036

6. Fave X, Cook M, Frederick A, *et al*. Preliminary investigation into sources of uncertainty in quantitative imaging features. *Comput Med Imaging Graph*. 2015;44:54-61.

   doi: 10.1016/j.compmedimag.2015.04.006

7. Zhao B, Tan Y, Tsai WY, *et al*. Reproducibility of radiomics for deciphering tumor phenotype with imaging. *Sci Rep*. 2016;6:23428.

   doi: 10.1038/srep23428

8. Mackin D, Fave X, Zhang L, *et al*. Measuring computed tomography scanner variability of radiomics features. *Invest Radiol*. 2015;50(11):757-65.

   doi: 10.1097/RLI.0000000000000180

9. Huynh E, Coroller TP, Narayan V, *et al*. Associations of radiomic data extracted from static and respiratory-gated CT scans with disease recurrence in lung cancer patients treated with SBRT. *PLoS One*. 2017;12(1):e0169172.

   doi: 10.1371/journal.pone.0169172

10. Kakino R, Nakamura M, Mitsuyoshi T, *et al.* Application and limitation of radiomics approach to prognostic prediction for lung stereotactic body radiotherapy using breath-hold CT images with random survival forest: A multi-institutional study. *Med Phys*. 2020;47(9):4634-4643.

    doi: 10.1002/mp.14380

11. Sawayanagi S, Yamashita H, Nozawa Y, *et al*. Establishment of a prediction model for overall survival after stereotactic body radiation therapy for primary non-small cell lung cancer using radiomics analysis. *Cancers* (*Basel*). 2022;14(16):3859.

    doi: 10.3390/cancers14163859

12. Luo LM, Huang BT, Chen CZ, *et al*. A combined model to improve the prediction of local control for lung cancer patients undergoing stereotactic body radiotherapy based on radiomic signature plus clinical and dosimetric parameters. *Front Oncol*. 2022;11:819047.

    doi: 10.3389/fonc.2021.819047

13. Isoyama-Shirakawa Y, Yoshitake T, Ninomiya K, *et al*. Combination of clinical factors and radiomics can predict local recurrence and metastasis after stereotactic body radiotherapy for non-small cell lung cancer. *Anticancer Res*. 2023;43(11):5003-5013.

    doi: 10.21873/anticanres.16699

14. Lafata KJ, Hong JC, Geng R, *et al*. Association of pre-treatment radiomic features with lung cancer recurrence following stereotactic body radiation therapy. *Phys Med Biol*. 2019;64(2):025007.

    doi: 10.1088/1361-6560/aaf5a5

15. Li Q, Kim J, Balagurunathan Y, Qi J, *et al*. CT imaging features associated with recurrence in non-small cell lung cancer patients after stereotactic body radiotherapy. *Radiat Oncol*. 2017;12(1):158.

    doi: 10.1186/s13014-017-0892-y

16. Na F, Wang J, Li C, Deng L, Xue J, Lu Y. Primary tumor standardized uptake value measured on F18-Fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non-small-cell lung cancer receiving radiotherapy: Meta-analysis. *J Thorac Oncol*. 2014;9(6):834-842.

    doi: 10.1097/JTO.0000000000000185

17. Agarwal M, Brahmanday G, Bajaj SK, Ravikrishnan KP, Wong CY. Revisiting the prognostic value of preoperative (18)F-fluoro-2-deoxyglucose ((18)F-FDG) positron emission tomography (PET) in early-stage (I & II) non-small cell lung cancers (NSCLC). *Eur J Nucl Med Mol Imaging*. 2010;37(4):691-698.

    doi: 10.1007/s00259-009-1291-x

18. Wu J, Aguilera T, Shultz D, *et al*. Early-stage non-small cell lung cancer: Quantitative imaging characteristics of (18)F fluorodeoxyglucose PET/CT allow prediction of distant metastasis. *Radiology*. 2016;281(1):270-278.

    doi: 10.1148/radiol.2016151829

19. Pyka T, Bundschuh RA, Andratschke N, *et al*. Textural features in pre-treatment [F18]-FDG-PET/CT are correlated with risk of local recurrence and disease-specific survival in early stage NSCLC patients receiving primary stereotactic

radiation therapy. *Radiat Oncol*. 2015;10:100.

doi: 10.1186/s13014-015-0407-7

20. Dissaux G, Visvikis D, Da-Ano R, *et al*. Pretreatment ^{18}F-FDG PET/CT radiomics predict local recurrence in patients treated with stereotactic body radiotherapy for early-stage non-small cell lung cancer: A multicentric study. *J Nucl Med*. 2020;61(6):814-820.

doi: 10.2967/jnumed.119.228106

21. Oikonomou A, Khalvati F, Tyrrell PN, *et al*. Radiomics analysis at PET/CT contributes to prognosis of recurrence and survival in lung cancer treated with stereotactic body radiotherapy. *Sci Rep*. 2018;8(1):4003.

doi: 10.1038/s41598-018-22357-y

22. Lucia F, Louis T, Cousin F, *et al*. Multicentric development and evaluation of [^{18}F]FDG PET/CT and CT radiomic models to predict regional and/or distant recurrence in early-stage non-small cell lung cancer treated by stereotactic body radiation therapy. *Eur J Nucl Med Mol Imaging*. 2024;51(4):1097-1108.

doi: 10.1007/s00259-023-06510-y

23. Nemoto H, Saito M, Satoh Y, *et al*. Evaluation of the performance of both machine learning models using PET and CT radiomics for predicting recurrence following lung stereotactic body radiation therapy: A single-institutional study. *J Appl Clin Med Phys*. 2024;25:e14322.

doi: 10.1002/acm2.14322

24. Zhang YP, Zhang XY, Cheng YT, *et al*. Artificial intelligence-driven radiomics study in cancer: The role of feature engineering and modeling. *Mil Med Res*. 2023;10(1):22.

doi: 10.1186/s40779-023-00458-8

25. Shen C, Liu Z, Guan M, *et al*. 2D and 3D CT radiomics features prognostic performance comparison in non-small cell lung cancer. *Transl Oncol*. 2017;10(6):886-894.

doi: 10.1016/j.tranon.2017.08.007

26. Zhu Y, Yao W, Xu BC, *et al*. Predicting response to immunotherapy plus chemotherapy in patients with esophageal squamous cell carcinoma using non-invasive radiomic biomarkers. *BMC Cancer*. 2021;21(1):1167.

doi: 10.1186/s12885-021-08899-x

27. Avanzo M, Wei L, Stancanello J, *et al*. Machine and deep learning methods for radiomics. *Med Phys*. 2020;47(5):e185-e202.

doi: 10.1002/mp.13678

28. Gao Y, Kalbasi A, Hsu W, *et al*. Treatment effect prediction for sarcoma patients treated with preoperative radiotherapy using radiomics features from longitudinal diffusion-weighted MRIs. *Phys Med Biol*. 2020;65(17):175006.

doi: 10.1088/1361-6560/ab9e58

29. Lorenz JW, Schott D, Rein L, *et al*. Serial T2-weighted magnetic resonance images acquired on a 1.5 tesla magnetic resonance linear accelerator reveal radiomic feature variation in organs at risk: An exploratory analysis of novel metrics of tissue response in prostate cancer. *Cureus*. 2019;11(4):e4510.

doi: 10.7759/cureus.4510

30. Mazzei MA, Nardone V, Di Giacomo L, *et al*. The role of delta radiomics in gastric cancer. *Quant Imaging Med Surg*. 2018;8(7):719-721.

doi: 10.21037/qims.2018.07.08

31. Ravanelli M, Agazzi GM, Tononcelli E, *et al*. Texture features of colorectal liver metastases on pretreatment contrast-enhanced CT may predict response and prognosis in patients treated with bevacizumab-containing chemotherapy: A pilot study including comparison with standard chemotherapy. *Radiol Med*. 2019;124(9):877-886.

doi: 10.1007/s11547-019-01046-4

32. 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(1):588.

doi: 10.1038/s41598-017-00665-z

33. Ma Y, Ma W, Xu X, Cao F. How does the delta-radiomics better differentiate pre-invasive GGNs from invasive GGNs? *Front Oncol*. 2020;10:1017.

doi: 10.3389/fonc.2020.01017

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 Oncol*. 2019;3:25.

doi: 10.1038/s41698-019-0096-z

35. Lin P, Yang PF, Chen S, *et al*. A Delta-radiomics model for preoperative evaluation of neoadjuvant chemotherapy response in high-grade osteosarcoma. *Cancer Imaging*. 2020;20(1):7.

doi: 10.1186/s40644-019-0283-8

36. Liu Y, Wu M, Zhang Y, *et al*. Imaging biomarkers to predict and evaluate the effectiveness of immunotherapy in advanced non-small-cell lung cancer. *Front Oncol*. 2021;11:657615.

doi: 10.3389/fonc.2021.657615

37. Colen RR, Rolfo C, Ak M, *et al*. Radiomics analysis for predicting pembrolizumab response in patients with advanced rare cancers. *J Immunother Cancer*. 2021;9(4):e001752.

doi: 10.1136/jitc-2020-001752

38. Fatima K, Dasgupta A, DiCenzo D, *et al*. Ultrasound delta-radiomics during radiotherapy to predict recurrence in patients with head and neck squamous cell carcinoma. *Clin Transl Radiat Oncol*. 2021;28:62-70.

doi: 10.1016/j.ctro.2021.03.002

39. 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 European Gastroenterol J*. 2016;4(2):257-263.

doi: 10.1177/2050640615601603

40. Goh V, Ganeshan B, Nathan P, Juttla JK, Vinayan A, Miles KA. Assessment of response to tyrosine kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. *Radiology*. 2011;261(1):165-171.

doi: 10.1148/radiol.11110264

41. Cunliffe A, Armato SG 3rd, Castillo R, Pham N, Guerrero T, Al-Hallaq HA. 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(5):1048-1056.

doi: 10.1016/j.ijrobp.2014.11.030

42. Keskinbora KH. Medical ethics considerations on artificial intelligence. *J Clin Neurosci*. 2019;64:277-282.

doi: 10.1016/j.jocn.2019.03.001

43. IEEE Global Initiative. A Vision for Prioritizing Human Well-being with Artificial Intelligence and Autonomous Systems. In: *The IEEE Global Initiative for Ethical Considerations in Artificial Intelligence and Autonomous Systems IEEE Glob Initiat Ethical Considerations*. Vol. 13. 2016.