Cancer Management and Research

Elevate Series

Open Access Full Text Article

REVIEW

Machine Learning in Diagnosis and Prognosis of Lung Cancer by PET-CT

Lili Yuan[1,*], Lin An[1,*], Yandong Zhu[1], Chongling Duan[1], Weixiang Kong[1], Pei Jiang[2], Qing-Qing Yu[1]

[1]Jining NO.1 People's Hospital, Shandong First Medical University, Jining, People's Republic of China; [2]Translational Pharmaceutical Laboratory, Jining NO.1 People's Hospital, Shandong First Medical University, Jining, People's Republic of China

*These authors contributed equally to this work

Correspondence: Qing-Qing Yu, Jining No.1 People's Hospital, Shandong First Medical University, Jining, 272000, People's Republic of China, Email yuqingqing_lucky@163.com; Pei Jiang, Translational Pharmaceutical Laboratory, Jining NO.1 People's Hospital, Shandong First Medical University, Jining, 272000, People's Republic of China, Email jiangpeicsu@sina.com

Abstract: As a disease with high morbidity and high mortality, lung cancer has seriously harmed people's health. Therefore, early diagnosis and treatment are more important. PET/CT is usually used to obtain the early diagnosis, staging, and curative effect evaluation of tumors, especially lung cancer, due to the heterogeneity of tumors and the differences in artificial image interpretation and other reasons, it also fails to entirely reflect the real situation of tumors. Artificial intelligence (AI) has been applied to all aspects of life. Machine learning (ML) is one of the important ways to realize AI. With the help of the ML method used by PET/CT imaging technology, there are many studies in the diagnosis and treatment of lung cancer. This article summarizes the application progress of ML based on PET/CT in lung cancer, in order to better serve the clinical. In this study, we searched PubMed using machine learning, lung cancer, and PET/CT as keywords to find relevant articles in the past 5 years or more. We found that PET/CT-based ML approaches have achieved significant results in the detection, delineation, classification of pathology, molecular subtyping, staging, and response assessment with survival and prognosis of lung cancer, which can provide clinicians a powerful tool to support and assist in critical daily clinical decisions. However, ML has some shortcomings such as slightly poor repeatability and reliability.

Keywords: machine learning, computed tomography, lung cancer, artificial intelligence, diagnosis

Introduction

Lung cancer remains the primary cause of death around the world.[1] Depending on the histological characteristics of the cancer cells microscopically, lung cancer can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with the former accounting for 85%. Common types of NSCLC include squamous cell carcinoma (SCC), adenocarcinoma (ADC), and large cell carcinoma (LCC).[2] Research shows that[3,4] the 5-year survival rate after diagnosis of lung cancer is less than 20%, and approximately 62–70% of patients are diagnosed with lung cancer at an advanced stage. The stage of lung malignancies at diagnosis determines its prognosis. In general, the 5-year survival rate of lung cancer in stage I can exceed 80%, but in stage IV, it is close to 0%.[5] Therefore, early diagnosis and treatment are crucial.[6] Positron emission tomography and computed tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG PET/CT, PET/CT for short) is an functional molecular imaging technology. As a non-invasive examination method, it can provide anatomical and functional information of multiple organs and tissues in the whole body, so it has been routinely used for the early identification, staging, and efficacy evaluation of tumors such as lung cancer, rectal cancer, ovarian cancer, breast cancer, and so on, which provides comprehensive diagnosis and treatment information.[7,8] The most widely used imaging agent for PET/CT examination in clinical practice is ^{18}F-FDG, which is a glucose analog. By combining the degree of tumor uptake with some semi-quantitative parameters provided by the instrument, it provides most characteristics of the tumor such as size, shape, internal structure, and relationship with surrounding tissues, so it can provide an important reference for tumor treatment and prognosis.[9] However, due to some special reasons, such as the heterogeneity of the tumor, some characteristics of the tumor which to a certain extent determine the response to treatment and their prognosis information have not been fully displayed according to the current treatment methods.

Received: 29 November 2023
Accepted: 16 April 2024
Published: 24 April 2024

Meanwhile, the current images are mostly interpreted manually, which is closely related to the experience of doctors. It is sometimes difficult to reach an agreement between different doctors. In addition, if the patient's preparation before imaging is not sufficient or the patients have recently undergone local surgery, radiotherapy, and chemotherapy, false-negative or false-positive results may appear on the PET/CT image.[10,11] Therefore, more advanced processing methods such as artificial intelligence (AI) are needed to assist in analyzing the imaging information of lesions.

AI refers to the use of computers and advanced technologies to simulate human intelligent behavior and critical thinking,[12] which has achieved great success in research and application.[13] AI includes many different technologies: intelligent agent,[14] symbolic and subsymbolic reasoning,[15] plan,[16] case-based reasoning,[17] fuzzy systems,[18] expert systems,[19] and so on. The tool that enables most of these techniques is machine learning (ML). ML is a technology that enables machines to imitate human behavior,[20] which can generate algorithms from a large number of databases and learn from experience, in other words, by developing some programs and mathematical algorithms that enable computers to program (build models) through experiential learning with or without human intervention, to make predictions and judgments on similar data.[21] Generally, the more the data, the better the model performance.[22] Therefore, ML model training requires powerful data storage and processing capabilities. ML contains four commonly used learning methods,[23–25] be called reinforcement learning, supervised learning, unsupervised learning, and semi-supervised learning, each of which can be used to solve different tasks. Classic ML methods in practical applications include Support Vector Machines (SVM),[26] Random Forest (RF),[27] Decision trees (DT),[28] Logistic Regression (LR),[29] K-nearest neighbors (KNN),[30] Naive Bayes (NB), Backpropagation artificial neural network (BP-ANN),[31] Adaptive boosting (AdaBoost),[32] and so on. Most of the algorithms belong to the category of supervised learning. With the rapid growth of science and technology, a new research field has emerged in ML, that is, deep learning (DL). DL, built on top of artificial neural networks, is a complex ML algorithm that mimics how the brain processes information, achieving far better results in speech and image recognition than previous technologies. The common method in DL is the neural network system based on convolution operation called fully convolutional network (FCN), convolutional neural network (CNN), generative adversarial network (GAN), recurrent neural network (RNN), and so on.[33] Among them, CNN has a wide range of applications.[34–37] It is a convolutional operation and downsampling or pooling operation of artificial neural networks based on depth architecture and multi-layer feedforward neural network, which accepts three-dimensional images as input. It can be trained end-to-end by a supervised method when learning highly discriminative image features. Since convolution operation is mainly used to process data with a grid-like structure, CNN has significant advantages in the analysis and recognition of time series and image data.[38]

The ML process can be divided into five steps: data acquisition; data preprocessing; model training; model verification and model use, each part of which covers more content and is no longer detailed here. The following words will be used in the practical application of ML, and it is necessary to explain them. The training set is the data used to train the model, the validation set is the data used to optimize the hyperparameters of the model, and the test set is the data used to evaluate the generalization ability of the model. The performance of the general model is evaluated through the confusion matrix, K-S value, AR value, receiver operating characteristic (ROC) curve, and area under curve (AUC). More and more research focus on the application of ML in tumor,[39–41] but by far, lung cancer is almost the most extensively studied and characterized malignancies.[42] Many studies have confirmed that PET/CT-based ML can be used for lung tumor recognition, tumor description, diagnosis and differential diagnosis, tumor staging, risk prediction, prognosis assessment, and early role prediction after treatment.[43–50] Horizontal exploration, such as identification of pathological types, gene mutations, immunohistochemical expression, and prediction of lymph node metastasis. The other category is longitudinal exploration, predicting possible future events, such as efficacy and prognostic predictions. This paper is to summarize the application of PET/CT-based ML methods in lung cancer in recent years (as shown in Figure 1). At present, ^{18}F-FDG is mostly used as a PET/CT imaging agent. There are few studies on other imaging agents, so the former is generally introduced without special explanation in this paper.

Tumor Detection

Studies[51] have shown that the proportion of malignancy in lung nodules is as high as 6.34%, and the five-year survival rate for early-stage lung cancer with surgical intervention can exceed 90%, so the early and definite diagnosis of lung cancer is of great significance. Although many studies[52–54] have confirmed the important role of PET/CT in distinguishing benign and

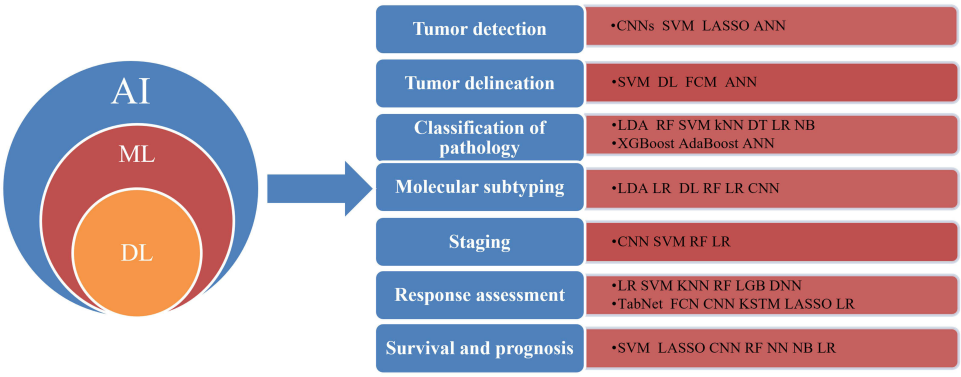

Figure 1 Application of PET/ CT-based ML in lung cancer. The relationship between AI, ML, and DL and the actual use of ML methods in the diagnosis and treatment of lung cancer.

malignant pulmonary nodules, there are some false-positive results such as granulomatous inflammation, organizing pneumonia, or other rare benign lesions, so it is necessary to combine other means to reduce the false-positive rate to avoid over-treatment and waste of medical resources. Therefore, the ML method has been used by many scholars[55] for the early recognition of carcinoma of the lungs. They have achieved a series of results. For PET-CT research of lung cancer, most of them[56] obtain diagnostic and radiological features automatically, but they always locate tumors manually. There are few studies[57,58] that use (ML) to combine automatic segmentation and extraction of lung lesion radiological data. Therefore, some scholars[59] who used two CNNs, the Detection CNN and Organ CNN to study PET/CT images of lung cancer, found that it could detect 90% of lung cancer and the level of automatic segmentation and extraction data by ML method was close to that of manual extraction, so it is suggested that the future research may be carried out instead of manual work. Another significance of the study was that negative lesions can be screened using the ML method, so clinicians can pay attention to those potentially malignant lesions, which can improve the efficiency of clinical treatment.

The research continues. Some researchers have applied the Least absolute shrinkage and selection operator (LASSO) method on PET/CT images to reduce the false-positive rate in lung malignant tumor diagnosis.[60] Meanwhile, SVM was also used to analyze the image information of 135 PET/CT patients, and it was found that Surface Volume Ratio and SUV peak had the potential ability to distinguish benign and malignant lung lesions.[61] Some scholars used the dynamic threshold segmentation method to recognize the pulmonary parenchyma in CT images and the suspicious regions in PET images, and then the dubious areas on the CT images were marked using the improved watershed method. Next, SVM was applied to classify pulmonary nodules. Based on the metabolic features of PET images and texture features of CT images, the sensitivity was higher than that of traditional CT methods, reaching 95.6%, and the false-positive rate was low.[62] Dual-time point imaging (DTPI) can enhance the accuracy of differentiating benign and malignant lesions in PET/CT. In a study,[63] SVM modeling was applied to analyze the characteristics of early and delayed PET/CT imaging, which showed higher accuracy and specificity than traditional PET/CT and CT in distinguishing benign and malignant solitary pulmonary nodules (SPNs). Quantitative indicators frequently used in PET/CT in clinical work or research are standard uptake value (SUV max) and metabolically active tumor volume (MTV). However, due to the heterogeneity of tumor shape and uptake, the tumor characteristics cannot be fully described.[64] In addition, SUV max $\geq$ 2.5 was used as the diagnostic threshold for malignant SPNs in the past, and the diagnostic efficiency of which was slightly insufficient under some conditions.[65] Therefore, some studies[66] have established an SVM model based on texture features to improve the diagnostic evidence of PET/CT in malignant SPNs larger than 5 mL, with an index AUC (95% CI) of 0.854 (0.637–1) which was better than traditional SUV max and MTV metrics. In addition to traditional ML methods, DL also plays a vital role in the early identification of lung malignant tumor. A research[67] analyzed the information of traditional CT and PET/CT of enrolled cases, established a deep transfer learning (TL) model based on ResNet-18, and found that the performance of the model built using traditional CT was better than that of the CT model in PET/CT. However, data information extracted from PET/CT, including size and SUV max of the pulmonary lesions, can enhance the performance of the DL system and increase the accuracy of PET/CT diagnosis of malignant tumor. CNN also plays a vital role in the

detection of lung tumors, based on a study of 104 PET-CT images of lung nodules. The study found that using CNN reduced the false-positive rate for lung cancer, from 72.8 to 4.9 per case.[68] Another scholar[69] used an artificial neural network (ANN) to analyze 18 cases of pure wool glass turbidity on PET/CT images, and compared the ability to explore malignant lesions with that of two blind specialists. It was found that ANN had a good predictive value, the AUC of which was 0.98 ± 0.02. As we all know, the use of PET/CT imaging is partly subject to its high dose, which is mainly from the radiation emitted by the imaging agent and the CT instrument itself. Therefore, some scholars used the ANN method to perform PET/CT imaging at three scanning doses, namely a standard dose of PET100%, 10% standard PET dose of PET10%, and PET3.3%, to detect lung cancer. The results showed that the AUC at the three doses were 0.989, 0.983, and 0.970, respectively. At the same time, it was found that the sensitivity and specificity of the (ML) method at the standard dose and PET3.3% dose were 95.9% and 91.5%, respectively, and the specificity was 98.1% and 94.2%. Therefore, it was concluded that ML may still be able to better detect lung cancer at lower PET/CT injection dose, which offered a new choice in clinical practice.[70]

Tumor Delineation

After the discovery of the tumor, its accurate description is of great significance for its precision treatment. In recent years, the method of ML has penetrated this field and achieved ideal results. Traditional PET has low spatial resolution and cannot fully describe tumor lesions, so a physics-guided modular DL frame work has been developed for automated tumor segmentation and has been used to accurately characterize primary lung tumors in PET images through small clinical training datasets, which demonstrated the ability to segment small tumors.[71] In other studies,[72] SVM technology was used to train the outline of gross tumor volumes (GTV) on PET/CT images based on optimal contour selection to distill the initial GTV region. The study found that the 3D dice similarity coefficient (DSC) can reach 0.777, suggesting that this technology can be used as an effective tool to determine tumor GTV.

DL has limitations in the application process, that is, model training requires a large amount of data. To solve this problem, a research team[73] integrated the Few Shot Learning (FSL) scheme into the U-Net architecture used for the segmentation of carcinoma of lung lesions on PET/CT scans, permitting dynamic model weight fine-tuning. In addition, an online supervised study plan was created, and the weight of the model was continuously adjusted online according to feedback from users, to increase the accuracy of detection and category, then better detection results were achieved. Through this research, clinicians could more accurately find the size, configuration, and position of the lung cancer and so forth to better serve the clinic.

Radiation therapy (referred to as radiotherapy) is a conventional treatment for lung cancer, and the precise delineation of its target area directly affects its therapeutic effect. PET/CT provides information on the biological activity of the tumor by obtaining the metabolic changes of the tumor, which can be used as an important reference for making radiotherapy plans. However, when PET/CT is routinely used to scan lung tumors, especially lung cancer lesions, due to the influence of respiratory movement, the lung tumors will be slightly displaced, which directly affects the accurate detection of tumors, and then affects the formulation of treatment, especially radiotherapy plans. To reduce the impact of tumor movement, SVM was used to[74] automatically depict the tumor starting with the first frame. With the help of the level set (LS) deformation model, the dimension and position information of the first was applied to track its movement in succeeding frames, so that the tumor volume of all frames could be accurately depicted, thus planning accurate and effective radiotherapy scope. Another study[75] included 60 NSCLC patients accepting stereotactic body radiation therapy (SBRT). In this research, PET and CT images of patients were sent to 3D DL fully convolutional networks (DFCN), and a co-segmentation model based upon PET/CT images was established. The study found that the various indicators of model were superior to manual segmentation and models on the strength of PET or CT images individual. Because of the heterogeneity of the tumor, the anatomical and metabolism from PET/CT may not fully reflect the true structure of the tumor. Therefore, studies[76] have compared three different ML methods fuzzy-c-means clustering method (FCM), ANN, and SVM to establish an automated fralanguage to describe the GTV of lung cancer lesions in PET/CT with stereotactic body radiation therapy. The results showed that various quantitative indicators such as DSC based on the FCM framework were superior to the other two methods, which also provided a method to accurately depict tumors to be more conducive to the formulation of precision radiotherapy plans in the future.

Classification of Pathology

After the tumor is accurately described, the next step is to consider its treatment, but attention must be paid to the subtype of NSCLC before treatment. The most common subtypes of NSCLC are SCC and ADC. It has been reported that different subtypes of NSCLC have different responses to the same treatment.[77] Therefore, it is important to distinguish NSCLC subtypes before treatment.[78,79] CT-guided needle biopsy is usually used to diagnose the pathological type, its numerous risks, sampling errors, and non-invasive limit its use. Sometimes this process is achieved with the help of PET/CT, as PET/CT imaging agents vary with different subtypes. However, it is sometimes difficult to distinguish NSCLC subtypes by PET/CT. Therefore, scholars have carried out many studies with the help of ML methods on PET/CT, and a series of results have been achieved in both traditional ML methods and DL, which will be introduced in detail below.

Researchers first explored a linear discriminant analysis (LDA) classifier combined with PET/CT images to distinguish NSCLC subtypes. Because of the small number of enrolled clients in the research, only 30 cases, the conclusions have not been widely considered in clinical practice.[80] Later, scholars[81] tried to use RF and gradient lift tree models to extract seven kinds of radiomics features extracted from PET/CT images of lung cancer. The results showed that combining image-omics methods was helpful in identifying ADC and SCC. DL methods are also commonly studied and are considered significantly superior to all traditional ML algorithms.[82]

In addition to using a single ML method for research, some scholars also included multiple ML methods at the same time, trying to find which method is more effective in distinguishing NSCLC subtypes. In this study,[83] 1417 patients with NSCLC were enrolled. Ten ML models, such as LDA, SVM, RF, and the VGG16 DL algorithm, were used to extract and analyze PET/CT image features to distinguish the subtypes. It was found that the VGG16 DL algorithm was better than other models. Other scholars[84] used LR, kNN, DT, and RF to further analyze the PET/CT image characteristics of patients with Phase I and II NSCLC. They found that the model built by kNN and LR had better performance than other methods, because it was in the nonlinear cutting space of kNN, but it had the risk of overfitting, and LR could reduce the risk of overfitting. Both methods were able to distinguish between ADC and SCC. Two different PET/CT scanners were used during the study, so they also found that differences in the instruments could affect the results described above. Shenet al[85] divided the tumor into multiple subregions according to the tracer metabolism and anatomical structure in PET/CT images. Based on the subregion image and traditional tumor image, seven classifiers were used to build a model to distinguish ADC and SCC. It was found that the performance of the subregion imaging model was superior to that of the tumor region imaging model. The optimal model is SVM with the radial basis function kernel (SVM-RBF) model, with sensitivity, specificity, accuracy, and AUC of 0.8538, 0.8758, 0.8623, and 0.9155, separately.

The clinical characteristics and laboratory indicators of patients play a key role in differentiating ADC from SCC, which can be further enhanced when both are included in ML studies.[86] Therefore, some scholars[87] used all kinds of ML learning skills, including LR, LDA, Naive Bayes (NB), KNN, SVM with radial basis function kernel, DT, RF, eXtreme Gradient Boosting (XGBoost), AdaBoost, and ANN combined clinical characteristics and part of laboratory indicators to build model to distinguish the two based on PET/CT radiomics feature. It is found that regardless of the training set or the verification set, the RF model with AUC 0.863 and SVM model with AUC 0.876 have the best diagnostic performance and can better distinguish the two. This study has a better effect than only combining clinical characteristics. Moreover, the study also found that the SVM model is more suitable for small samples, and the RF model is more suitable for situations where there is data loss in the study. Given the difference in glucose metabolism between ADC and SCC,[88] therefore, researchers[89] have used a variety of ML methods (RF, neural network, NB, LR, and SVM) to study PET/CT image features of lung cancer. Some clinical characteristics of the subjects, which include age, sex, tumor size, and smoking status, were also introduced. The results indicated that the LR model had better predictive ability than other models (AUC = 0.859, accuracy = 0.769, precision = 0.804) which can distinguish well between pulmonary ADC and SCC. The study also found that Sex, SUV max, gray-level zone length nonuniformity, gray-level nonuniformity for zone, and total lesion glycolysis were the optimum predictors of pulmonary ADC.

Further studies[90] showed that the prognosis of different ADC subtypes at the same TNM stage may be different, which is determined by the characteristics of histological progression and the main growth pattern. Some scholars tried to use the Dedicaid Automated ML platform combined with PET/CT images of ADC patients and some clinical data, to establish a prediction model for long-term survival outcome and histological features of initially treated ADC patients. In

this study, the 4-year and 3-year tumor grade (TG), overall survival (OS), and histologic growth pattern risk (GPR) of enrolled patients were analyzed. It was found that all parameters responded well, with the highest AUC of 0.88. This study provides a non-invasive means of obtaining ADC subtypes.

Molecular Subtyping

Before treatment of lung cancer, attention should be paid to its efficacy, so we need to find influence factors. Among those factors, one of which is the epidermal growth factor receptor (EGFR) mutation. There are various driver mutations in NSCLC,[91] incorporating oncogenic mutations such as EGFR, BRAF, ROS1, MET, and ALK. EGFR mutations are more common.[92] If targeted therapy can be carried out for patients with these mutations, compared with traditional chemotherapy, the progression-free survival rate will be increased, and the quality of life will be improved.[93] Since the mutation information is usually obtained through invasive means such as surgery or puncture with many side effects, a non-invasive prediction method is needed. Some scholars[94] tried to extract texture characteristic from CT and PET/CT images of NSCLC patients, with the help of Linear discriminant analysis (LDA) and multivariate LR to establish models. Leave-one-out Cross Validation (LOOCV) was used to validate the model to identify and distinguish EGFR mutation types. The results showed that the model built from PET/CT images had a higher AUC, which may be related to the better tumor segmentation achieved by taking more imaging agents in tumor tissues. However, the tissue surrounding the tumor in CT affected the segmentation. This study has achieved a good prediction effect, which may guide clinical treatment.

Targeted therapy as immune checkpoint inhibitors (ICI) acting on programmed death-1 (PD-1) receptor on T cells or the programmed death ligand-1 (PD-L1) expressed by tumor cells and tyrosine kinase inhibitors (TKI) acting on EGFR are usually used in NSCLC.[95] However, studies have shown that whether EGFR is mutated or not has different sensitivity to EGFR- TKI treatment,[96] which plays a vital role in the targeted therapy of NSCLC,[97] especially related to the efficacy of the treatment.[98] It is therefore crucial to identify EGFR mutations pretherapy.[99]

The ^{18}F-labeled small-molecule PET imaging molecular probe ^{18}F-MPG has been used by some scholars to identify mutated EGFR to screen patients who would benefit from TKI therapy, but as the imaging agents used were too difficult to obtain, it has not been extensively studied.[100] Later, some scholars[101] used PET/CT images to establish a DL model, such as small-residual-convolutional neural network (SResCNN) to predict the mutation state of EGFR. EGFR-deep learning score (DLS) was formed to find out which patients could benefit from the two treatments. In this study, the AUC of training, validation, and independent test cohorts were 0.86, 0.83, and 0.81, respectively. At the same time, some researchers used ResNet DL to analyze the PET/CT image features of NSCLC patients in combination with major clinical data, for example, age, gender, and smoking history to build models to predict EGFR mutations whose results are satisfactory. The cases in this study were from multiple centers. The study also pointed out that the combination of patients clinical data was better than the simple analysis of PET/CT image feature modeling in which case prediction sensitivity and accuracy, with AUC ranging from 0.81 to 0.85, sensitivity and accuracy ranging from 0.60 to 0.76 and 0.82 to 0.83, respectively. The "lower-level" prediction models were integrated to the "higher-level" model more effectively by using stacked generalization in the study.[102]

Research on EGFR mutations continues. LASSO was used by some studies in ML to analyze the PET/CT image features of ADC patients, together with some clinical data to create a model to make predictions about the performance of OS in EGFR-positive stage III and IV patients who have previously received systemic therapy. Satisfactory results were achieved.[103] RF and LR were used to build a prediction model based on PET/CT, and satisfactory results were obtained over the prediction of EGFR mutations. It is AUCs fluctuated from 0.77 to 0.92.[104] Yip[105] et al used MATLAB software and eight PET imaging features to successfully predict EGFR mutation in 348 NSCLC patients and could also predict the prognosis of NSCLC patients after chemotherapy.[106] The above research results avoid non-invasive operations to obtain the information on EGFR mutations, and offer a reference for implementation of EGFR-TKI for the treatment of lung cancer.

More and more studies have proven that for patients with advanced NSCLC, immune blockers targeting PD-1 or PD-L1 can achieve better survival rates than traditional chemotherapy.[107,108] Therefore, PD-L1 inhibitors have become the standard treatment for some NSCLC patients. PD-L1 is the only clinically approved marker that triggers ICIs therapy, which is usually achieved through invasive procedures. Some studies[109,110] have found that by using SResCNN to analyze PET/CT imaging and clinical information of NSCLC to build DLS to predict the presentation of PD-L1 in pulmonary malignancy. So it can provide pre-treatment advice for patients who need immunotherapy.

Staging

As we all know, the different stages of the disease are closely related to the prognosis of the neoplasm.[111] Other things being equal, those who are at the highest risk of lung cancer death benefit the most from early detection,[112] and the earlier the stage, the more appropriate treatment, the better the effect. So early identification is more important, providing additional opportunities to provide cure and prevent death from carcinoma of the lungs.[113] PET/CT can be used as a significant imaging technique for clinical staging in lung cancer,[114] with the help of ML,[115–118] its application ability is further improved, which is described below.

Lymph node metastasis is a crucial criterion for clinical staging in lung cancer. Some researchers use PET/CT radiomics to distinguish benign and malignant lymph nodes to help stage lung cancer.[119] Other scholars have used different ML and DL means to identify metastasis of mediastinal lymph node in NSCLC patients with PET/CT and achieved ideal results.[120] At present, CNN is extensively used in the staging of malignant tumor of the lung. The CNN algorithm was used in some studies with PET/CT image data to divide 472 cases into stages T1-T2 or T3-T4. And then cases were included in the training set (n = 303), verification set (n = 75), together with test set (n = 94) teams. The results found that the accuracy rate [correct/(correct + incorrect)] in the training, verification, and test sets was 87%, 86%, and 90%, separately, suggesting the important role of CNN in staging.[121] Other researchers used CNN to predict lymph nodes and distant metastases of NSCLC based on PET/CT, and found that CNN performed well in predicting the N stage, with a prediction accuracy of 0.80.[122] Therefore, CNN is expected to be used as a staging tool for lung cancer in the immediate future.

People who develop NSCLC with stage I generally have a better prognosis than those with stage II and III.[123] Traditional ML research on lung cancer staging often adopts a single method, and the prediction effect varies with a different method. If different ML methods are integrated, the final prediction efficiency will be improved. Therefore, researchers have used the fusion of SVM, RF, and LR to analyze PET/CT image features, and found that the prediction efficiency is higher than that of a single method. By predicting stages II and III of NSCLC, we can identify patients who will benefit from subsequent treatment.[124]

Response Assessment

The choice of tumor treatment is of great significance to its prognosis. Therefore, accurate and reliable decision-making on tumor prognosis can help to plan appropriate treatment programs such as surgery, chemoradiotherapy, targeting, immunotherapy, and so on, and improve patient management according to different stages of the disease.[125]

Sublobar resection was confirmed to be an effective treatment for primary lung cancer, but some studies found that for highly invasive cancer, this resection method could increase the local recurrence rate of lung cancer compared with lobectomy,[126] therefore, if highly invasive cancer can be identified before surgery, appropriate treatment can be selected. The tumor invasiveness is usually assessed by the tumor diameter and consolidation tumor ratio (CTR) in CT images;[127] however, CT findings do not completely correspond to pathological findings.[128] So scholars began to explore new methods. Some experts used ML methods to study PET/CT and CT image data of primary lung cancer undergoing lobectomy or segmentectomy to evaluate the aggressiveness of lung cancer. This study used seven ML methods such as LR, SVM, RF, KNN, light gradient boosting (LGB),[129] deep neural net (DNN), together with TabNet,[130] to establish the ensemble model (ENS) individually and jointly. All models performed well, with LR and ENS having better predictive performance than other models. At the same time, the prediction performance of the PET/CT patterns was superior to that of CT.[131]

For some lung cancer patients who have lost the chance of surgery, radiotherapy and chemotherapy have become the main means of treatment. If the therapeutic effect can be predicted, the treatment plan can be adjusted in time, and mortality from lung cancer can be reduced. Metabolic tumor volume 50% (MTV50) > 4.04 in PET/CT was found to be a separate predictor of poor prognostic features in NSCLC patients undergoing chemotherapy using ML,[132] which can be used as a biological marker to predict chemotherapy sensitivity and effectiveness of NSCLC patients. The application of ML in radiotherapy is discussed below. Radiotherapy plans that determine the efficacy rely heavily on image segmentation. Some studies used 3D fully convolutional neural networks (FCN), including CT and PET data, to realize automatic multimodal image segmentation. This method was robust. Its effectiveness was also confirmed by 84 cases of lung cancer.[133] U-net, as one of the most favorite image segmentation architectures of CNN, can be used to self-act segment apparatus at risk in radiotherapy for lung cancer. The morphological and metabolic data provided by PET/CT fusion

imaging is utilized to improve the accuracy and radiotherapy effect of lung cancer.[134–136] SBRT is currently believed to be the criterion treatment for patients with early stage of lung cancer who are medically impractical or refuse surgical operation.[137] The kernel support tensor machine (KSTM) has been used to predict the prognosis of early NSCLC receiving SBRT. Certain results have been achieved.[138] Another study using supervised principal component analysis found that mixed PET-CT imaging features improved the prediction of relapse after SBRT treatment.[139]

Immunotherapy is an emerging treatment for lung cancer in recent years. It is a promising approach through immune checkpoint blockade. It has been reported that only a few patients can get great benefit from immunotherapy.[140] Therefore, it is important to predict the outcome of immunotherapy pretherapy. At present, many studies have proven that the neoplasm immune microenvironment (TIME) affects the efficacy of immunotherapy.[141–144] Therefore, some scholars have used the LASSO logistic regression method to build PET/CT imaging and clinical features such as gender, smoking history, and SUVmax model of NSCLC patients, to reflect TIME phenotypes by predicting the expression of CD8 in tumor tissues to predict the patient's response to immunotherapy.[145] Some results have been obtained.

Survival and Prognosis

Scholars and experts agree[146,147] that recurrence of NSCLC after comprehensive treatment is an important factor affecting its survival rate, especially within 2 years after curative intent therapy.[148,149] In the past, recurrence was detected mainly through regular follow-up means, including the detection of tumor markers and imaging examinations such as PET/CT examination, and so on. However, due to the heterogeneity of tumors, the aggressiveness of tumor cells will change during treatment, so the prediction ability of the above means is limited. The mortality rate of NSCLC will reduce if some means, such as ML, can be used to predict recurrence early, so timely treatment is given.[150–152] The application of ML is not only to process and analyze image data but also to store and record more patient-related information, which can help doctors make personalized medical decisions for patients, understand patients' treatment responses, and predict survival rates. Studies have revealed that the combined application of the CT model and PET model established with ML is better than that applied alone in predicting the local recurrence of NSCLC.[153,154]

Some scholars[155] used linear SVM to train the PET/CT image features of 30 NSCLC patients and established a new feature set, called size-aware longitudinal pattern (SALoP). After 2 years of follow-up after the last treatment of the patients, it was found to be superior to the traditional radiomic method in predicting prognosis. At the same time, there were also studies[156] using the LASSO program to preprocess PET/CT images, and then utilizing an extracted texture features by the gray-level co-occurrence matrix (GLCM), which was found to be an individual predictor of overall survival of lung cancer. When together with genetic and clinical information, the overall performance of prognostic features was higher.[157] DL has also been studied in this area. Some scholars analyzed pre-treated PET/CT data with the help of CNN and found that it performed well in predicting lung malignant tumor progression and OS. Meanwhile, this study also used a random survival forests (RSF) model based on DL characteristics, which may be associated with meaningful areas and margins of lesions.[158]

Single ML has performed well in predicting the recurrence of lung cancer. Therefore, some scholars have tried to use a variety of ML methods to build a prognostic model of lung cancer to determine whether it can help identify factors affecting the development and outcome of tumors, to correctly evaluate the effect of treatment measures.[159] Studies are using six different ML methods: SVM, RF, neural network, naive Bayes, LR, and gradient boosting to analyze the PET/CT imaging features to establish a model for predicting the recurrence of NSCLC after treatment. It was found that the naive Bayes model had the optimum predictive ability, which had an AUC of 0.816. Imaging features such as Gray level size zone matrix-low-intensity short-zone emphasis (GLSZM-LISZE) together with GLSZM-high-intensity zone emphasis (HIZE) extracted from PET/CT were superior to other features in predicting the recurrence of tumors than.[160]

In addition to the conventional use of ML to establish predictive models, in recent years, scholars have found that the body composition phenotype may be related to the immune function of the body, thus affecting the therapeutic efficacy and survival of patients.[161,162] Further studies[163] have found that the cross-sectional muscle area of the lumbar 3 vertebrae is closely related to the overall muscle mass. Based on the L3 vertebral body level, there were at least three phenotypes of physical compositions, containing visceral fat area (VFA), subcutaneous fat area (SFA), together with skeletal muscle index (SMI) are associated with the prognosis of NSCLC patients.[164–166] Based on the above research, some scholars[167] used the least absolute shrinkage and selection operator (LASSO) with ten-fold cross-validation methods for the purpose of obtaining state

IV NSCLC baseline PET/CT imaging features, to establish a comprehensive prediction model by combining the above three body component features to get prognostic prediction of patients with advanced NSCLC. They found that the combined prediction model improved the ability to predict progression-free survival in patients with NSCLC in IV stage possessing AUC values of 0.803 and 0.866 in the training and validation sets, separately, compared with the body phenotype or imaging omics prediction models alone.

Conclusions

The data cited in this review mainly came from the following sources: searches of common databases such as PubMed, Medline (Ovid), EMBASE, Google Scholar, and the Cochrane Library on related topics; some research centers, and projects such as cancer screening programs. Multicentric Italian Lung Detection (MILD) trial, a single center in the inflammatory-endemic region, Yale Cancer Center, Princess Margaret Cancer Centre, Veterans Health Service Medical Center, VU University Medical Center, the Cancer Genome Atlas (TCGA) cohort, and American College of Radiology Imaging Network (ACRIN) 6668/Radiation Therapy Oncology Group (RTOG) 0235; institutional databases such as government datasets, Lung Image Database Consortium (LIDC) database, Lung-PET-CT-Dx open dataset from The Cancer Imaging Archive Database (TCIA), the Kaiser Permanente Southern California (KPSC) Cancer Registry and Research Data Warehouse, institutional lung cancer database, public repositories, and local medical institutions. Some of these studies and clinical trials experienced one, two, or even 10 years.

Despite the increasing use of ML in the diagnosis and treatment of lung cancer, there are still some shortcomings. First, interpretability is a challenge in ML applications. An important reason for this is that most ML models do not explicitly identify causal features and simply rely on correlating input features with outcomes, which can lead to unexpected outcomes and uncertain behavior. High-risk medical decisions, such as diagnosis, treatment, and prognostic choices, require interpretable decision-making processes. There is limited interpretability in most ML models, meaning it is difficult to understand how millions of parameters work simultaneously. If clinicians cannot explain how a technique reached a certain conclusion, patients may not have the confidence to accept the results of ML. The second problem is the repeatability of the model. A single dataset was used by most studies for model development and validation, which has a certain degree of bias, and the conclusions may not be applicable to all cases. DL, in particular, is limited by the amount and quality of data used to train the model. Last but not least, many doctors are afraid that their jobs will be replaced by ML, so they are unwilling to accept or even reject this technology from the heart, which hinders the application of ML in clinical practice. From the perspective of the imaging physician, this development should not be seen as a threat, but rather as an opportunity to play a pioneering role in the health care sector and actively shape this transformation process. Machines do not have the ability to have such complex conversations as humans, and the empathy to match that of doctors, which remains an important aspect of the doctor's role.

In the future, clinicians in particular will need to shift their thinking to embrace ML technology, familiarize them with the basic concepts and metrics, increase collaboration with developers and help develop it to meet appropriate clinical needs, who adapt their daily practices to ensure ML works in company with them which is not a threat to their role. At the same time, we actively develop and integrate databases, improve existing ML algorithms and create new ML algorithms, establish comprehensive quality control and standardization tools, data sharing and verification of multi-institutional data to standardize their processes, in order to achieve more efficient and accurate diagnosis, to realize the important role of ML in the diagnosis and treatment of tumors.

Abbreviations

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma; large cell carcinoma, LCC; AI, artificial intelligence; SVM, Support Vector Machines; RF, Random Forest; DT, Decision trees; LR, Logistic Regression; KNN, K-nearest neighbors; NB, Naive Bayes; BP-ANN, Backpropagation artificial neural network; AdaBoost, Adaptive boosting; FCN, fully convolutional network; CNN, convolutional neural network; GAN, generative adversarial network; RNN, recurrent neural network; ROC, receiver operating characteristic; AUC, area under the curve; MTV, tumor volume; GTV, gross tumor volumes; FSL, Few Shot Learning; LS, level set; SBRT, stereotactic body radiation therapy; LDA, linear discriminant analysis; NB, Naive Bayes; GPR, growth pattern

risk; EGFR, epidermal growth factor receptor; LOOCV, Leave-one-out Cross Validation; TKI, tyrosine kinase inhibitors; CTR, consolidation tumor ratio; RSF, random survival forests; GLSZM-LISZE, Gray level size zone matrix-low-intensity short-zone emphasis; VFA, containing visceral fat area; SFA, subcutaneous fat area; SMI, skeletal muscle index.

Acknowledgments

This work was supported by the grant of the Key R&D Program of Jining (no. 2023YXNS051).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Coche E, Lonneux M, Geets X. Lung cancer: morphological and functional approach to screening, staging and treatment planning. *Future Oncol*. 2010;6(3):367–380. doi:10.2217/fon.10.7
2. Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. *Mayo Clin Proc*. 2019;94(8):1623–1640. doi:10.1016/j.mayocp.2019.01.013
3. Jones GS, Baldwin DR. Recent advances in the management of lung cancer. *Clin Med*. 2018;18(Suppl 2):s41–s46. doi:10.7861/clinmedicine.18-2-s41
4. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *New Engl J Med*. 2020;382(6):503–513. doi:10.1056/NEJMoa1911793
5. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) Edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39–51. doi:10.1016/j.jtho.2015.09.009
6. Arbour KC, Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA*. 2019;322(8):764–774. doi:10.1001/jama.2019.11058
7. Kapoor V, McCook BM, Torok FS. An introduction to PET-CT imaging. *Radiographics*. 2004;24(2):523–543. doi:10.1148/rg.242025724
8. Hoffmann B, Frenzel T, Schmitz R, Schumacher U, Wedemann G. Modeling Growth of tumors and their spreading behavior using mathematical functions. *Methods Mol Biol*. 2019;1878:263–277.
9. Wisnivesky JP, Henschke C, McGinn T, Iannuzzi MC. Prognosis of Stage II non-small cell lung cancer according to tumor and nodal status at diagnosis. *Lung Cancer*. 2005;49(2):181–186. doi:10.1016/j.lungcan.2005.02.010
10. Szyszko TA, Yip C, Szlosarek P, Goh V, Cook GJ. The role of new PET tracers for lung cancer. *Lung Cancer*. 2016;94:7–14. doi:10.1016/j.lungcan.2016.01.010
11. Iravani A, Turgeon GA, Akhurst T, et al. PET-detected pneumonitis following curative-intent chemoradiation in non-small cell lung cancer (NSCLC): recognizing patterns and assessing the impact on the predictive ability of FDG-PET/CT response assessment. *Eur J Nucl Med Mol Imaging*. 2019;46(9):1869–1877. doi:10.1007/s00259-019-04388-3
12. Amisha Malik P, Pathania M, Rathaur VK. Overview of artificial intelligence in medicine. *J Fam Med Prim Care*. 2019;8(7):2328–2331. doi:10.4103/jfmpc.jfmpc_440_19
13. Mintz Y, Brodie R. Introduction to artificial intelligence in medicine. *Minimally Invasive Ther Allied Technol*. 2019;28(2):73–81. doi:10.1080/13645706.2019.1575882
14. Milne-Ives M, de Cock C, Lim E, et al. The effectiveness of artificial intelligence conversational agents in health care: systematic review. *J Med Int Res*. 2020;22(10):e20346. doi:10.2196/20346
15. Han Z, Wei B, Xi X, Chen B, Yin Y, Li S. Unifying neural learning and symbolic reasoning for spinal medical report generation. *Med Image Anal*. 2021;67:101872. doi:10.1016/j.media.2020.101872
16. Schwalbe N, Wahl B. Artificial intelligence and the future of global health. *Lancet*. 2020;395(10236):1579–1586. doi:10.1016/S0140-6736(20)30226-9
17. van Zijl A, van Loon M, ten Cate O. Case-Based clinical reasoning in practice. In: ten Cate O, Custers E, Durning SJ, editors. *Principles and Practice of Case-Based Clinical Reasoning Education: A Method for Preclinical Students*. Cham (CH): Springer Copyright 2018, The Author(s); 2018:75–83.
18. Vlamou E, Papadopoulos B. Neuro-fuzzy networks and their applications in medical fields. *Adv Exp Med Biol*. 2020;1194:437.
19. Ao C, Jin S, Ding H, Zou Q, Yu L. Application and development of artificial intelligence and intelligent disease diagnosis. *Curr Pharm Des*. 2020;26(26):3069–3075. doi:10.2174/1381612826666200331091156
20. Greener JG, Kandathil SM, Moffat L, Jones DT. A guide to machine learning for biologists. *Nat Rev Mol Cell Biol*. 2022;23(1):40–55. doi:10.1038/s41580-021-00407-0
21. Martín Noguerol T, Paulano-Godino F, Martín-Valdivia MT, Menias CO, Luna A. Strengths, weaknesses, opportunities, and threats analysis of artificial intelligence and machine learning applications in radiology. *J Am College Radiol*. 2019;16(9 Pt B):1239–1247. doi:10.1016/j.jacr.2019.05.047
22. Handelman GS, Kok HK, Chandra RV, Razavi AH, Lee MJ, Asadi H. eDoctor: machine learning and the future of medicine. *J Internal Med*. 2018;284(6):603–619. doi:10.1111/joim.12822
23. Aslin RN. Statistical learning: a powerful mechanism that operates by mere exposure. Wiley interdisciplinary reviews. *Cognit Sci*. 2017;8(1–2). doi:10.1002/wcs.1373
24. Jiang T, Gradus JL, Rosellini AJ. Supervised Machine learning: a brief primer. *Behav Ther*. 2020;51(5):675–687. doi:10.1016/j.beth.2020.05.002
25. Choi RY, Coyner AS, Kalpathy-Cramer J, Chiang MF, Campbell JP. Introduction to machine learning, neural networks, and deep learning. *Trans Vision Sci Technol*. 2020;9(2):14.

26. Rodríguez-Pérez R, Bajorath J. Evolution of support vector machine and regression modeling in chemoinformatics and drug discovery. *J Comput Aided Molec Design*. 2022;36(5):355–362. doi:10.1007/s10822-022-00442-9
27. Hu J, Szymczak S. A review on longitudinal data analysis with random forest. *Briefings Bioinf*. 2023;24(2). doi:10.1093/bib/bbad002
28. Karalis G. Decision Trees and Applications. *Adv Exp Med Biol*. 2020;1194:239–242.
29. Schober P, Vetter TR. Logistic regression in medical research. *Anesthesia Analg*. 2021;132(2):365–366. doi:10.1213/ANE.0000000000005247
30. Zhang Z. Introduction to machine learning: k-nearest neighbors. *Ann Translat Med*. 2016;4(11):218. doi:10.21037/atm.2016.03.37
31. Heng SY, Ridwan WM, Kumar P, et al. Artificial neural network model with different backpropagation algorithms and meteorological data for solar radiation prediction. *Sci Rep*. 2022;12(1):10457. doi:10.1038/s41598-022-13532-3
32. Zheng Z, Yang Y. Adaptive boosting for domain adaptation: toward robust predictions in scene segmentation. *IEEE Trans Image Process*. 2022;31:5371–5382. doi:10.1109/TIP.2022.3195642
33. Jiang Y, Yang M, Wang S, Li X, Sun Y. Emerging role of deep learning-based artificial intelligence in tumor pathology. *Cancer Commun*. 2020;40(4):154–166. doi:10.1002/cac2.12012
34. Araújo T, Aresta G, Castro E, et al. Classification of breast cancer histology images using convolutional neural networks. *PLoS One*. 2017;12(6):e0177544. doi:10.1371/journal.pone.0177544
35. Derry A, Krzywinski M, Altman N. Convolutional neural networks. *Nature Methods*. 2023;20(9):1269–1270. doi:10.1038/s41592-023-01973-1
36. Wang L, Ding L, Liu Z, et al. Automated identification of malignancy in whole-slide pathological images: identification of eyelid malignant melanoma in gigapixel pathological slides using deep learning. *Br J Ophthalmol*. 2020;104(3):318–323. doi:10.1136/bjophthalmol-2018-313706
37. Ehteshami Bejnordi B, Mullooly M, Pfeiffer RM, et al. Using deep convolutional neural networks to identify and classify tumor-associated stroma in diagnostic breast biopsies. *Mod Pathol*. 2018;31(10):1502–1512. doi:10.1038/s41379-018-0073-z
38. Ciompi F, Chung K, van Riel SJ, et al. Towards automatic pulmonary nodule management in lung cancer screening with deep learning. *Sci Rep*. 2017;7(1):46479. doi:10.1038/srep46479
39. Liu Z, Wang S, Dong D, et al. The applications of radiomics in precision diagnosis and treatment of oncology: opportunities and challenges. *Theranostics*. 2019;9(5):1303–1322. doi:10.7150/thno.30309
40. 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
41. Deist TM, Dankers F, Valdes G, et al. Machine learning algorithms for outcome prediction in (chemo)radiotherapy: an empirical comparison of classifiers. *Med Phys*. 2018;45(7):3449–3459. doi:10.1002/mp.12967
42. Shi L, He Y, Yuan Z, et al. Radiomics for response and outcome assessment for non-small cell lung cancer. *Technol Cancer Res Treat*. 2018;17:1533033818782788. doi:10.1177/1533033818782788
43. Nensa F, Demircioglu A, Rischpler C. Artificial intelligence in nuclear medicine. *J Nucl Med*. 2019;60(Suppl 2):29s–37s. doi:10.2967/jnumed.118.220590
44. Seifert R, Weber M, Kocakavuk E, Rischpler C, Kersting D. Artificial intelligence and machine learning in nuclear medicine: future perspectives. *Semi Nucl Med*. 2021;51(2):170–177. doi:10.1053/j.semnuclmed.2020.08.003
45. Lee LIT, Kanthasamy S, Ayyalaraju RS, Ganatra R. The current state of artificial intelligence in medical imaging and nuclear medicine. *BJR Open*. 2019;1(1):20190037. doi:10.1259/bjro.20190037
46. Ninatti G, Kirienko M, Neri E, Sollini M, Chiti A. Imaging-based prediction of molecular therapy targets in NSCLC by radiogenomics and AI approaches: a systematic review. *Diagnostics*. 2020;10(6):359. doi:10.3390/diagnostics10060359
47. Lv Z, Fan J, Xu J, et al. Value of (18)F-FDG PET/CT for predicting EGFR mutations and positive ALK expression in patients with non-small cell lung cancer: a retrospective analysis of 849 Chinese patients. *Eur J Nucl Med Mol Imaging*. 2018;45(5):735–750. doi:10.1007/s00259-017-3885-z
48. Tran KA, Kondrashova O, Bradley A, Williams ED, Pearson JV, Waddell N. Deep learning in cancer diagnosis, prognosis and treatment selection. *Genome Med*. 2021;13(1):152. doi:10.1186/s13073-021-00968-x
49. Sadaghiani MS, Rowe SP, Sheikhbahaei S. Applications of artificial intelligence in oncologic (18)F-FDG PET/CT imaging: a systematic review. *Ann Translat Med*. 2021;9(9):823. doi:10.21037/atm-20-6162
50. Swanson K, Wu E, Zhang A, Alizadeh AA, Zou J. From patterns to patients: advances in clinical machine learning for cancer diagnosis, prognosis, and treatment. *Cell*. 2023;186(8):1772–1791. doi:10.1016/j.cell.2023.01.035
51. Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer screening, version 3.2018, NCCN clinical practice guidelines in oncology. *J National Compr Cancer Network*. 2018;16(4):412–441. doi:10.6004/jnccn.2018.0020
52. Fletcher JW, Kymes SM, Gould M, et al. A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. *J Nucl Med*. 2008;49(2):179–185. doi:10.2967/jnumed.107.044990
53. Ruilong Z, Daohai X, Li G, Xiaohong W, Chunjie W, Lei T. Diagnostic value of 18F-FDG-PET/CT for the evaluation of solitary pulmonary nodules: a systematic review and meta-analysis. *Nuclear med commun*. 2017;38(1):67–75. doi:10.1097/MNM.0000000000000605
54. Li ZZ, Huang YL, Song HJ, Wang YJ, Huang Y. The value of 18F-FDG-PET/CT in the diagnosis of solitary pulmonary nodules: a meta-analysis. *Medicine*. 2018;97:12.
55. Sim Y, Chung MJ, Kotter E, et al. Deep convolutional neural network-based software improves radiologist detection of malignant lung nodules on chest radiographs. *Radiology*. 2020;294(1):199–209. doi:10.1148/radiol.2019182465
56. Kirienko M, Gallivanone F, Sollini M, et al. FDG PET/CT as theranostic imaging in diagnosis of non-small cell lung cancer. *Front Biosci*. 2017;22(10):1713–1723. doi:10.2741/4567
57. Soufi M, Kamali-Asl A, Geramifar P, Rahmim A. A novel framework for automated segmentation and labeling of homogeneous versus heterogeneous lung tumors in [(18)F]FDG-PET imaging. *Mole Imag Biol*. 2017;19(3):456–468. doi:10.1007/s11307-016-1015-0
58. Bug D, Feuerhake F, Oswald E, Schüler J, Merhof D. Semi-automated analysis of digital whole slides from humanized lung-cancer xenograft models for checkpoint inhibitor response prediction. *Oncotarget*. 2019;10(44):4587–4597. doi:10.18632/oncotarget.27069
59. Borrelli P, Ly J, Kaboteh R, et al. AI-based detection of lung lesions in [(18)F]FDG PET-CT from lung cancer patients. *EJNMMI Phys*. 2021;8(1):32. doi:10.1186/s40658-021-00376-5
60. Wang K, Qiao Z, Zhao X, et al. Individualized discrimination of tumor recurrence from radiation necrosis in glioma patients using an integrated radiomics-based model. *Eur J Nucl Med Mol Imaging*. 2020;47(6):1400–1411. doi:10.1007/s00259-019-04604-0

61. Zhang R, Zhu L, Cai Z, et al. Potential feature exploration and model development based on 18F-FDG PET/CT images for differentiating benign and malignant lung lesions. *Eur J Radiol*. 2019;121:108735. doi:10.1016/j.ejrad.2019.108735
62. Zhao J, Ji G, Qiang Y, Han X, Pei B, Shi Z. A new method of detecting pulmonary nodules with PET/CT based on an improved watershed algorithm. *PLoS One*. 2015;10:4.
63. Chen S, Harmon S, Perk T, et al. Diagnostic classification of solitary pulmonary nodules using dual time (18)F-FDG PET/CT image texture features in granuloma-endemic regions. *Sci Rep*. 2017;7(1):9370. doi:10.1038/s41598-017-08764-7
64. Visvikis D, Hatt M, Tixier F, Cheze Le Rest C. The age of reason for FDG PET image-derived indices. *Eur J Nucl Med Mol Imaging*. 2012;39 (11):1670–1672. doi:10.1007/s00259-012-2239-0
65. Alkhawaldeh K, Bural G, Kumar R, Alavi A. Impact of dual-time-point (18)F-FDG PET imaging and partial volume correction in the assessment of solitary pulmonary nodules. *Eur J Nucl Med Mol Imaging*. 2008;35(2):246–252. doi:10.1007/s00259-007-0584-1
66. Zhang J, Ma G, Cheng J, Song S, Zhang Y, Shi LQ. Diagnostic classification of solitary pulmonary nodules using support vector machine model based on 2-[18F]fluoro-2-deoxy-D-glucose PET/computed tomography texture features. *Nuclear Med Commun*. 2020;41(6):560–566. doi:10.1097/MNM.0000000000001193
67. Park YJ, Choi D, Choi JY, Hyun SH. Performance evaluation of a deep learning system for differential diagnosis of lung cancer with conventional CT and FDG PET/CT using transfer learning and metadata. *Clin Nucl Med*. 2021;46(8):635–640. doi:10.1097/RLU.0000000000003661
68. Teramoto A, Fujita H, Yamamuro O, Tamaki T. Automated detection of pulmonary nodules in PET/CT images: ensemble false-positive reduction using a convolutional neural network technique. *Med Phys*. 2016;43(6):2821–2827. doi:10.1118/1.4948498
69. Scott JA, McDermott S, Kilcoyne A, Wang Y, Halpern EF, Ackman JB. Comparison of (18)F-FDG avidity at PET of benign and malignant pure ground-glass opacities: a paradox? Part II: artificial neural network integration of the PET/CT characteristics of ground-glass opacities to predict their likelihood of malignancy. *Clin Radiol*. 2019;74(9):692–696. doi:10.1016/j.crad.2019.04.024
70. Schwyzer M, Ferraro DA, Muehlematter UJ, et al. Automated detection of lung cancer at ultralow dose PET/CT by deep neural networks - Initial results. *Lung Cancer*. 2018;126:170–173. doi:10.1016/j.lungcan.2018.11.001
71. Leung KH, Marashdeh W, Wray R, et al. A physics-guided modular deep-learning based automated framework for tumor segmentation in PET. *Phys Med Biol*. 2020;65(24):245032. doi:10.1088/1361-6560/ab8535
72. Ikushima K, Arimura H, Jin Z, et al. Computer-assisted framework for machine-learning-based delineation of GTV regions on datasets of planning CT and PET/CT images. *J Radiat Res*. 2017;58(1):123–134. doi:10.1093/jrr/rrw082
73. Protonotarios NE, Katsamenis I, Sykiotis S, et al. A few-shot U-Net deep learning model for lung cancer lesion segmentation via PET/CT imaging. *Biomed Phys Eng Express*. 2022;8(2):025019. doi:10.1088/2057-1976/ac53bd
74. Gubbi J, Kanakatte A, Tomas K, et al. Automatic tumour volume delineation in respiratory-gated PET images. *J Med Imag Radiat Oncol*. 2011;55(1):65–76. doi:10.1111/j.1754-9485.2010.02231.x
75. Zhong Z, Kim Y, Plichta K, et al. Simultaneous cosegmentation of tumors in PET-CT images using deep fully convolutional networks. *Med Phys*. 2019;46(2):619–633. doi:10.1002/mp.13331
76. Kawata Y, Arimura H, Ikushima K, et al. Impact of pixel-based machine-learning techniques on automated frameworks for delineation of gross tumor volume regions for stereotactic body radiation therapy. *Phys Med*. 2017;42:141–149. doi:10.1016/j.ejmp.2017.08.012
77. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist*. 2009;14(3):253–263. doi:10.1634/theoncologist.2008-0232
78. Khosravi P, Kazemi E, Imielinski M, Elemento O, Hajirasouliha I. Deep convolutional neural networks enable discrimination of heterogeneous digital pathology images. *EBioMedicine*. 2018;27:317–328. doi:10.1016/j.ebiom.2017.12.026
79. Feng P, Shao Z, Dong B, et al. Application of diffusion kurtosis imaging and (18)F-FDG PET in evaluating the subtype, stage and proliferation status of non-small cell lung cancer. *Front Oncol*. 2022;12:989131. doi:10.3389/fonc.2022.989131
80. Ha S, Choi H, Cheon GJ, et al. Autoclustering of non-small cell lung carcinoma subtypes on (18)F-FDG PET using texture analysis: a preliminary result. *Nucl Med molec Imag*. 2014;48(4):278–286. doi:10.1007/s13139-014-0283-3
81. Koyasu S, Nishio M, Isoda H, Nakamoto Y, Togashi K. Usefulness of gradient tree boosting for predicting histological subtype and EGFR mutation status of non-small cell lung cancer on (18)F FDG-PET/CT. *Ann Nucl Med*. 2020;34(1):49–57. doi:10.1007/s12149-019-01414-0
82. Ren C, Zhang J, Qi M, et al. Correction to: machine learning based on clinico-biological features integrated 18F-FDG PET/CT radiomics for distinguishing squamous cell carcinoma from adenocarcinoma of lung. *Eur J Nucl Med Mol Imaging*. 2021;48(5):1696. doi:10.1007/s00259-021-05226-1
83. Han Y, Ma Y, Wu Z, et al. Histologic subtype classification of non-small cell lung cancer using PET/CT images. *Eur J Nucl Med Mol Imaging*. 2021;48(2):350–360. doi:10.1007/s00259-020-04771-5
84. Dondi F, Gatta R, Albano D, et al. Role of radiomics features and machine learning for the histological classification of stage I and stage II NSCLC at [(18)F]FDG PET/CT: a comparison between two PET/CT scanners. *J Clin Med*. 2022;12(1). doi:10.3390/jcm12010255
85. Shen H, Chen L, Liu K, et al. A subregion-based positron emission tomography/computed tomography (PET/CT) radiomics model for the classification of non-small cell lung cancer histopathological subtypes. *Quantit Imag Med Surg*. 2021;11(7):2918–2932. doi:10.21037/qims-20-1182
86. Yang G, Xiao Z, Tang C, Deng Y, Huang H, He Z. Recent advances in biosensor for detection of lung cancer biomarkers. *Biosens Bioelectron*. 2019;141:111416. doi:10.1016/j.bios.2019.111416
87. Zhao H, Su Y, Wang M, et al. The machine learning model for distinguishing pathological subtypes of non-small cell lung cancer. *Front Oncol*. 2022;12:875761. doi:10.3389/fonc.2022.875761
88. Koh YW, Lee SJ, Park SY. Differential expression and prognostic significance of GLUT1 according to histologic type of non-small-cell lung cancer and its association with volume-dependent parameters. *Lung Cancer*. 2017;104:31–37. doi:10.1016/j.lungcan.2016.12.003
89. Hyun SH, Ahn MS, Koh YW, Lee SJ. A machine-learning approach using PET-based radiomics to predict the histological subtypes of lung cancer. *Clin Nucl Med*. 2019;44(12):956–960. doi:10.1097/RLU.0000000000002810
90. Zhao M, Kluge K, Papp L, et al. Multi-lesion radiomics of PET/CT for non-invasive survival stratification and histologic tumor risk profiling in patients with lung adenocarcinoma. *Eur Radiol*. 2022;32(10):7056–7067. doi:10.1007/s00330-022-08999-7
91. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311 (19):1998–2006. doi:10.1001/jama.2014.3741

92. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Canc Res*. 2015;5(9):2892–2911.
93. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol*. 2016;17(5):577–589. doi:10.1016/S1470-2045(16)30033-X
94. Nair JKR, Saeed UA, McDougall CC, et al. Radiogenomic models using machine learning techniques to predict EGFR mutations in non-small cell lung cancer. *Can Assoc Radiol J*. 2021;72(1):109–119. doi:10.1177/0846537119899526
95. Sha L, Osinski BL, Ho IY, et al. Multi-field-of-view deep learning model predicts nonsmall cell lung cancer programmed death-ligand 1 status from whole-slide hematoxylin and eosin images. *J Pathol Inform*. 2019;10(1):24. doi:10.4103/jpi.jpi_24_19
96. Truini A, Starrett JH, Stewart T, et al. The EGFR exon 19 mutant L747-A750>P exhibits distinct sensitivity to tyrosine kinase inhibitors in lung adenocarcinoma. *Clin Cancer Res*. 2019;25(21):6382–6391. doi:10.1158/1078-0432.CCR-19-0780
97. An N, Zhang Y, Niu H, et al. EGFR-TKIs versus taxanes agents in therapy for nonsmall-cell lung cancer patients: a PRISMA-compliant systematic review with meta-analysis and meta-regression. *Medicine*. 2016;95(50):e5601. doi:10.1097/MD.0000000000005601
98. Giatromanolaki A, Koukourakis IM, Balaska K, Mitrakas AG, Harris AL, Koukourakis MI. Programmed death-1 receptor (PD-1) and PD-ligand-1 (PD-L1) expression in non-small cell lung cancer and the immune-suppressive effect of anaerobic glycolysis. *Med Oncol*. 2019;36(9):76. doi:10.1007/s12032-019-1299-4
99. Coudray N, Ocampo PS, Sakellaropoulos T, et al. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. *Nature Med*. 2018;24(10):1559–1567. doi:10.1038/s41591-018-0177-5
100. Sun X, Xiao Z, Chen G, et al. A PET imaging approach for determining EGFR mutation status for improved lung cancer patient management. *Sci Trans Med*. 2018;10(431). doi:10.1126/scitranslmed.aan8840
101. Mu W, Jiang L, Zhang J, et al. Non-invasive decision support for NSCLC treatment using PET/CT radiomics. *Nat Commun*. 2020;11(1):5228. doi:10.1038/s41467-020-19116-x
102. Chen S, Han X, Tian G, et al. Using stacked deep learning models based on PET/CT images and clinical data to predict EGFR mutations in lung cancer. *Front Med*. 2022;9:1041034. doi:10.3389/fmed.2022.1041034
103. Yang B, Ji H, Zhong J, et al. Value of (18)F-FDG PET/CT-based radiomics nomogram to predict survival outcomes and guide personalized targeted therapy in lung adenocarcinoma with EGFR mutations. *Front Oncol*. 2020;10:567160. doi:10.3389/fonc.2020.567160
104. Liu Q, Sun D, Li N, et al. Predicting EGFR mutation subtypes in lung adenocarcinoma using (18)F-FDG PET/CT radiomic features. *Transl Lung Canc Res*. 2020;9(3):549–562. doi:10.21037/tlcr.2020.04.17
105. Yip SS, Kim J, Coroller TP, et al. Associations between somatic mutations and metabolic imaging phenotypes in non-small cell lung cancer. *J Nucl Med*. 2017;58(4):569–576. doi:10.2967/jnumed.116.181826
106. Krarup MMK, Nygård L, Vogelius IR, et al. Heterogeneity in tumours: validating the use of radiomic features on (18)F-FDG PET/CT scans of lung cancer patients as a prognostic tool. *Radiother Oncol*. 2020;144:72–78. doi:10.1016/j.radonc.2019.10.012
107. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124–128. doi:10.1126/science.aaa1348
108. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *New Engl J Med*. 2016;375(19):1823–1833. doi:10.1056/NEJMoa1606774
109. Jiang M, Sun D, Guo Y, et al. Assessing PD-L1 expression level by radiomic features from PET/CT in nonsmall cell lung cancer patients: an initial result. *Acad Radiol*. 2020;27(2):171–179. doi:10.1016/j.acra.2019.04.016
110. Mu W, Jiang L, Shi Y, et al. Non-invasive measurement of PD-L1 status and prediction of immunotherapy response using deep learning of PET/CT images. *J Immunother Canc*. 2021;9(6):e002118. doi:10.1136/jitc-2020-002118
111. Park HJ, Park N, Lee JH, et al. Automated extraction of information of lung cancer staging from unstructured reports of PET-CT interpretation: natural language processing with deep-learning. *BMC Med Inf Decis Making*. 2022;22(1):229. doi:10.1186/s12911-022-01975-7
112. Bach PB, Gould MK. When the average applies to no one: personalized decision making about potential benefits of lung cancer screening. *Ann Internal Med*. 2012;157(8):571–573. doi:10.7326/0003-4819-157-8-201210160-00524
113. Choi HS, Jeong BK, Jeong H, et al. Application of the new 8th TNM staging system for non-small cell lung cancer: treated with curative concurrent chemoradiotherapy. *Radiat Oncol*. 2017;12(1):122. doi:10.1186/s13014-017-0848-2
114. Zhong Z, Kim Y, Buatti J, Wu X. 3D alpha matting based co-segmentation of tumors on PET-CT images. *Molecu Imag Reconstr Analy Mov Body Organs Stroke Imag Treat*. 2017;10555:31–42.
115. Yoo J, Cheon M, Park YJ, et al. Machine learning-based diagnostic method of pre-therapeutic (18)F-FDG PET/CT for evaluating mediastinal lymph nodes in non-small cell lung cancer. *Eur Radiol*. 2021;31(6):4184–4194. doi:10.1007/s00330-020-07523-z
116. Mercan C, Aksoy S, Mercan E, Shapiro LG, Weaver DL, Elmore JG. Multi-instance multi-label learning for multi-class classification of whole slide breast histopathology images. *IEEE Transact Med Imag*. 2018;37(1):316–325. doi:10.1109/TMI.2017.2758580
117. Zeune LL, de Wit S, Berghuis AMS, Terstappen L, Brune C. How to agree on a CTC: evaluating the consensus in circulating tumor cell scoring. *Cytometry*. 2018;93(12):1202–1206. doi:10.1002/cyto.a.23576
118. Gould MK, Huang BZ, Tammemagi MC, Kinar Y, Shiff R. Machine learning for early lung cancer identification using routine clinical and laboratory data. *Am J Respir Crit Care Med*. 2021;204(4):445–453. doi:10.1164/rccm.202007-2791OC
119. Kirienko M, Cozzi L, Rossi A, et al. Ability of FDG PET and CT radiomics features to differentiate between primary and metastatic lung lesions. *Eur J Nucl Med Mol Imaging*. 2018;45(10):1649–1660. doi:10.1007/s00259-018-3987-2
120. Rogasch JMM, Michaels L, Baumgärtner GL, et al. A machine learning tool to improve prediction of mediastinal lymph node metastases in non-small cell lung cancer using routinely obtainable [18F]FDG-PET/CT parameters. *Eur J Nucl Med Mol Imaging*. 2023;50(7):2140–2151. doi:10.1007/s00259-023-06145-z
121. Kirienko M, Sollini M, Silvestri G, et al. Convolutional neural networks promising in lung cancer T-parameter assessment on baseline FDG-PET/CT. *Contrast Media Mole Imag*. 2018;2018:1382309. doi:10.1155/2018/1382309
122. Tau N, Stundzia A, Yasufuku K, Hussey D, Metser U. Convolutional neural networks in predicting nodal and distant metastatic potential of newly diagnosed non-small cell lung cancer on FDG PET images. *Am J Roentgenol*. 2020;215(1):192–197. doi:10.2214/AJR.19.22346

123. Desseroit MC, Visvikis D, Tixier F, et al. Erratum to: development of a nomogram combining clinical staging with 18F-FDG PET/CT image features in non-small-cell lung cancer stage I-III. *Eur J Nucl Med Mol Imaging*. 2016;43(10):1933. doi:10.1007/s00259-016-3450-1
124. Sepehri S, Tankyevych O, Upadhaya T, Visvikis D, Hatt M, Cheze Le Rest C. Comparison and fusion of machine learning algorithms for prospective validation of PET/CT radiomic features prognostic value in stage II-III non-small cell lung cancer. *Diagnostics*. 2021;11(4):675. doi:10.3390/diagnostics11040675
125. Yoo J, Lee J, Cheon M, et al. Predictive Value of (18)F-FDG PET/CT using machine learning for pathological response to neoadjuvant concurrent chemoradiotherapy in patients with stage III non-small cell lung cancer. *Cancers*. 2022;14(8):1987. doi:10.3390/cancers14081987
126. Koike T, Koike T, Yoshiya K, Tsuchida M, Toyabe S. Risk factor analysis of locoregional recurrence after sublobar resection in patients with clinical stage IA non-small cell lung cancer. *J Thoracic Cardiovasc Surg*. 2013;146(2):372–378. doi:10.1016/j.jtcvs.2013.02.057
127. Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg*. 2002;74(5):1635–1639. doi:10.1016/S0003-4975(02)03895-X
128. Aokage K, Miyoshi T, Ishii G, et al. Clinical and pathological staging validation in the eighth edition of the TNM classification for lung cancer: correlation between solid size on thin-section computed tomography and invasive size in pathological findings in the new T classification. *J Thorac Oncol*. 2017;12(9):1403–1412. doi:10.1016/j.jtho.2017.06.003
129. Du Z, Zhong X, Wang F, Uversky VN. Inference of gene regulatory networks based on the light gradient boosting machine. *Comput Biol Chem*. 2022;101:107769. doi:10.1016/j.compbiolchem.2022.107769
130. Zheng X, He B, Hu Y, et al. Diagnostic accuracy of deep learning and radiomics in lung cancer staging: a systematic review and meta-analysis. *Front Public Health*. 2022;10:938113. doi:10.3389/fpubh.2022.938113
131. Onozato Y, Iwata T, Uematsu Y, et al. Predicting pathological highly invasive lung cancer from preoperative [(18)F]FDG PET/CT with multiple machine learning models. *Eur J Nucl Med Mol Imaging*. 2023;50(3):715–726. doi:10.1007/s00259-022-06038-7
132. Li X, Wang D, Yu L. Prognostic and Predictive values of metabolic parameters of (18)F-FDG PET/CT in patients with non-small cell lung cancer treated with chemotherapy. *Molec Imag*. 2019;18:1536012119846025. doi:10.1177/1536012119846025
133. Zhao X, Li L, Lu W, Tan S. Tumor co-segmentation in PET/CT using multi-modality fully convolutional neural network. *Phys Med Biol*. 2018;64(1):015011. doi:10.1088/1361-6560/aaf44b
134. Lustberg T, van Soest J, Gooding M, et al. Clinical evaluation of atlas and deep learning based automatic contouring for lung cancer. *Radiother Oncol*. 2018;126(2):312–317. doi:10.1016/j.radonc.2017.11.012
135. Zhou X. Automatic Segmentation of multiple organs on 3D CT images by using deep learning approaches. *Adv Exp Med Biol*. 2020;1213:135–147.
136. Zhong Z, Kim Y, Zhou L, et al. 3D Fully convolutional networks for co-segmentation of tumors on pet-Ct images. *IEEE Int Sympos Biomed Imag*. 2018;2018:228–231.
137. Mattonen SA, Palma DA, Haasbeek CJ, Senan S, Ward AD. Early prediction of tumor recurrence based on CT texture changes after stereotactic ablative radiotherapy (SABR) for lung cancer. *Med Phys*. 2014;41(3):033502. doi:10.1118/1.4866219
138. Li S, Yang N, Li B, et al. A pilot study using kernelled support tensor machine for distant failure prediction in lung SBRT. *Med Image Anal*. 2018;50:106–116. doi:10.1016/j.media.2018.09.004
139. 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
140. Mezquita L, Auclin E, Ferrara R, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. *JAMA Oncol*. 2018;4(3):351–357. doi:10.1001/jamaoncol.2017.4771
141. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature*. 2017;541(7637):321–330. doi:10.1038/nature21349
142. Gajewski TF, Corrales L, Williams J, Horton B, Sivan A, Spranger S. Cancer immunotherapy targets based on understanding the T cell-inflamed versus non-T cell-inflamed tumor microenvironment. *Adv Exp Med Biol*. 2017;1036:19–31.
143. Binnewies M, Roberts EW, Kersten K, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nature Med*. 2018;24(5):541–550. doi:10.1038/s41591-018-0014-x
144. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat Rev Drug Discov*. 2019;18(3):197–218. doi:10.1038/s41573-018-0007-y
145. Tong H, Sun J, Fang J, et al. A machine learning model based on PET/CT Radiomics and clinical characteristics predicts tumor immune profiles in non-small cell lung cancer: a retrospective multicohort study. *Front Immunol*. 2022;13:859323. doi:10.3389/fimmu.2022.859323
146. Uramoto H, Tanaka F. Prediction of recurrence after complete resection in patients with NSCLC. *Anticancer Res*. 2012;32(9):3953–3960.
147. Huh JW, Kim CH, Lim SW, Kim HR, Kim YJ. Early recurrence in patients undergoing curative surgery for colorectal cancer: is it a predictor for poor overall survival? *Int J Colorec Dis*. 2013;28(8):1143–1149. doi:10.1007/s00384-013-1675-z
148. Lou F, Sima CS, Rusch VW, Jones DR, Huang J. Differences in patterns of recurrence in early-stage versus locally advanced non-small cell lung cancer. *Ann Thorac Surg*. 2014;98(5):1755–1760; discussion 1760–1751. doi:10.1016/j.athoracsur.2014.05.070
149. Kay FU, Kandathil A, Batra K, Saboo SS, Abbara S, Rajiah P. Revisions to the tumor, node, metastasis staging of lung cancer (8(th) edition): rationale, radiologic findings and clinical implications. *World J Radiol*. 2017;9(6):269–279. doi:10.4329/wjr.v9.i6.269
150. De Wever W, Ceyssens S, Mortelmans L, et al. Additional value of PET-CT in the staging of lung cancer: comparison with CT alone, PET alone and visual correlation of PET and CT. *Eur Radiol*. 2007;17(1):23–32. doi:10.1007/s00330-006-0284-4
151. Vu CC, Matthews R, Kim B, Franceschi D, Bilfinger TV, Moore WH. Prognostic value of metabolic tumor volume and total lesion glycolysis from ^{18}F-FDG PET/CT in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer. *Nuclear med commun*. 2013;34(10):959–963. doi:10.1097/MNM.0b013e32836491a9
152. Liu J, Dong M, Sun X, Li W, Xing L, Yu J. Prognostic value of 18F-FDG PET/CT in surgical non-small cell lung cancer: a meta-analysis. *PLoS One*. 2016;11:1.
153. Hosny A, Parmar C, Coroller TP, et al. Deep learning for lung cancer prognostication: a retrospective multi-cohort radiomics study. *PLoS Med*. 2018;15(11):e1002711. doi:10.1371/journal.pmed.1002711
154. Baek S, He Y, Allen BG, et al. Deep segmentation networks predict survival of non-small cell lung cancer. *Sci Rep*. 2019;9(1):17286. doi:10.1038/s41598-019-53461-2

155. Astaraki M, Wang C, Buizza G, Toma-Dasu I, Lazzeroni M, Smedby Ö. Early survival prediction in non-small cell lung cancer from PET/CT images using an intra-tumor partitioning method. *Phys Med*. 2019;60:58–65. doi:10.1016/j.ejmp.2019.03.024
156. Ohri N, Duan F, Snyder BS, et al. Pretreatment 18F-FDG PET textural features in locally advanced non-small cell lung cancer: secondary analysis of ACRIN 6668/RTOG 0235. *J Nucl Med*. 2016;57(6):842–848. doi:10.2967/jnumed.115.166934
157. Grossmann P, Stringfield O, El-Hachem N, et al. Defining the biological basis of radiomic phenotypes in lung cancer. *eLife*. 2017;3:6.
158. Huang B, Sollee J, Luo YH, et al. Prediction of lung malignancy progression and survival with machine learning based on pre-treatment FDG-PET/CT. *EBioMedicine*. 2022;82:104127. doi:10.1016/j.ebiom.2022.104127
159. He J, Zhang JX, Chen CT, et al. The relative importance of clinical and socio-demographic variables in prognostic prediction in non-small cell lung cancer: a variable importance approach. *Med Care*. 2020;58(5):461–467. doi:10.1097/MLR.0000000000001288
160. Park SB, Kim KU, Park YW, Hwang JH, Lim CH. Application of 18 F-fluorodeoxyglucose PET/CT radiomic features and machine learning to predict early recurrence of non-small cell lung cancer after curative-intent therapy. *Nucl Med Commun*. 2023;44(2):161–168. doi:10.1097/MNM.0000000000001646
161. Yi X, Chen Q, Yang J, et al. CT-Based sarcopenic nomogram for predicting progressive disease in advanced non-small-cell lung cancer. *Front Oncol*. 2021;11:643941. doi:10.3389/fonc.2021.643941
162. de Jong C, Chargi N, Herder GJM, et al. The association between skeletal muscle measures and chemotherapy-induced toxicity in non-small cell lung cancer patients. *J Cachexia Sarcope Musc*. 2022;13(3):1554–1564. doi:10.1002/jcsm.12967
163. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. *Semin Cell Dev Biol*. 2016;54:2–10. doi:10.1016/j.semcdb.2015.09.001
164. Sjøblom B, Grønberg BH, Wentzel-Larsen T, et al. Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer. *Clin Nutr*. 2016;35(6):1386–1393. doi:10.1016/j.clnu.2016.03.010
165. Oruc Z, Akbay A, Ali Kaplan M, et al. A low body fat mass ratio predicts poor prognosis in patients with advanced non-small cell lung cancer. *Nutr Cancer*. 2022;74(9):3284–3291. doi:10.1080/01635581.2022.2074064
166. Gezer NS, Bandos AI, Beeche CA, Leader JK, Dhupar R, Pu J. CT-derived body composition associated with lung cancer recurrence after surgery. *Lung Cancer*. 2023;179:107189. doi:10.1016/j.lungcan.2023.107189
167. Zhang Y, Tan W, Zheng Z, Wang J, Xing L, Sun X. Body composition and radiomics from 18F-FDG PET/CT together help predict prognosis for patients with stage IV non-small cell lung cancer. *J Comput Assist Tomogra*. 2023;47(6):906–912. doi:10.1097/RCT.0000000000001496