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(54) Title: METHODS AND SYSTEMS FOR PREDICTION OF CARDIOTOXICITY

(57) Abstract: Disclosed are radiomics and artificial-intelligence-based methods for predicting clinical cardiac assessment of FDG PET-CT scans. Certain embodiments use a computational method to extract features from one or more cardiac portions of diagnostic scans (e.g., FDG PET-CT scans). In certain embodiments, the method can use extracted features to predict cardiotoxicity for physician evaluation. In certain embodiments, the method can use the extracted features to predict for cardiac clinical complications. In certain embodiments, the method can enable early cardiac toxicity prediction for cancer patients using standard-of-care FDG PET-CT imaging. In certain embodiments, the method can provide a cardiac management decision support tool using standard-of-care FDG PET-CT imaging. In certain embodiments, the method can enable the incorporation of the extracted features in radiation treatment planning (e.g., for patients whose management involves radiation) using standard-of-care FDG PET-CT imaging.

WO 2025/101706 A1

METHODS AND SYSTEMS FOR PREDICTION OF CARDIOTOXICITY

CROSS-REFERENCE TO RELATED APPLICATION(S)

This application claims the benefit of priority to U.S. Provisional Patent Application Serial No. 63/596,788 entitled " METHODS AND SYSTEMS FOR PREDICTION OF CARDIOTOXICITY," filed November 7, 2023, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

The present disclosure generally relates to the field of artificial intelligence and functional imaging. In particular, the present disclosure is related to method and systems for prediction of cardiotoxicity.

BACKGROUND

Computed tomography (CT) scans and/or positron emission tomography (PET) scans are widely used in the medical industry to obtain detailed internal images of the body. Fluorodeoxyglucose (FDG) based positron emission tomography/computed tomography (PET/CT) imaging is routinely obtained as part of standard staging workup for cancer patients. The data from CT/PET scans and related diagnostic scans can provide invaluable insight into the recommended treatment protocol for a patient. A large amount of data is collected from CT/PET scans and related diagnostic scans at the outset of treatment and throughout treatment; however, much of the data collected from such scans is disregarded and/or not analyzed at the beginning of treatment.

Patients treated with cancer therapy can have cardiac complications due to treatment. Although FDG PET/CT scans are typically used to evaluate the tumor, imaging guidelines note that FDG PET/CT scans are an FDA-approved method to image for cardiac inflammation. Patients can have different cardiac FDG PET/CT distributions indicative of unique cardiac states. Currently, no automated methods exist to evaluate the cardiac signal in FDG PET/CT scans.

It would be desirable to provide a method and system to automatically evaluate the cardiac signal in diagnostic PET/CT scans.

DEFINITIONS

The instant invention is most clearly understood with reference to the following definitions.

As used herein, the singular form "a," "an," and "the" include plural references unless the context clearly dictates otherwise.

Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of standard tolerance in the art, for example, within 2 standard deviations of the mean. "About" can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

As used in the specification and claims, the terms "comprises," "comprising," "containing," "having," and the like can have the meaning ascribed to them in U.S. patent law and can mean "includes," "including," and the like.

Unless specifically stated or obvious from context, the term "or," as used herein, is understood to be inclusive.

Ranges provided herein are understood to be shorthand for all values within the field. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 (as well as fractions thereof unless the context clearly dictates otherwise).

BRIEF DESCRIPTION OF THE DRAWINGS

For a fuller understanding of the nature and desired objects of the present invention, reference is made to the following detailed description taken in conjunction with the accompanying drawing figures wherein like reference characters denote corresponding parts throughout the several views.

The invention is best understood from the following detailed description when read in connection with the accompanying drawings. It is emphasized that, according to common practice, the various features of the drawing are not to scale. On the contrary, the dimensions of the various features are arbitrarily deformed or reduced for clarity. Included in the drawings are the following figures.

FIG. 1 depicts an exemplary diagnostic scan (PET/CT scan) used in connection with various exemplary embodiments of the present disclosure.

FIGS. 2A-2C depicts portions of an exemplary diagnostic scan (PET/CT scan) illustrating uniform, non-uniform, and absent cardiac uptake, respectively.

FIGS. 3A-3D depicts different cardiac FDG PET/CT distributions indicative of different cardiac states.

FIG. 4 depicts a schematic block diagram of radiomics used in connection with an artificial intelligence (AI) model in accordance with an exemplary embodiment of the present disclosure.

FIG. 5 depicts a schematic block diagram of a system for predicting cardiotoxicity in accordance with an exemplary embodiment of the present disclosure.

FIG. 6 depicts a flow diagram of certain methods of the present disclosure, in accordance with an exemplary embodiment of the present disclosure.

FIG. 7 depicts a schematic block diagram of radiomics model building in accordance with an exemplary embodiment of the present disclosure.

FIG. 8 depicts a schematic block diagram of radiomics model inference in accordance with an exemplary embodiment of the present disclosure.

FIG. 9 depicts a schematic block diagram of radiomics model refinement in accordance with an exemplary embodiment of the present disclosure.

FIG. 10 depicts a schematic block diagram of an assessment of cardiotoxicity risk in accordance with an exemplary embodiment of the present disclosure.

FIG. 11 depicts a graphical representation of survival curves separated according to whether patients had an increase or decrease in cardiac SUV, in accordance with an exemplary embodiment of the present disclosure.

FIG. 12 depicts an illustrative representation of a representative patient example using FDG PET-CT to demonstrate abnormal uptake in the heart, in accordance with an exemplary embodiment of the present disclosure.

FIG. 13 depicts a metrics to be collected in a patient database in accordance with an exemplary embodiment of the present disclosure.

FIG. 14 depicts factors evaluated for cardiotoxicity prediction in accordance with an exemplary embodiment of the present disclosure.

FIG. 15 depicts a cardiac model diagram using training data set and external validation data sets, in accordance with an exemplary embodiment of the present disclosure.

FIG. 16 depicts a tree-based optimization tool for automating machine learning in accordance with an exemplary embodiment of the present disclosure.

DETAILED DESCRIPTION

The present disclosure describes methods of determining predicted cardiotoxicity and systems regarding the same. Provided herein are radiomics and artificial-intelligence-based methods for predicting clinical cardiac assessment of FDG PET-CT scans. Certain

embodiments of the present disclosure use a computational method to extract features from one or more cardiac portions of diagnostic scans (e.g., FDG PET-CT scans). In certain embodiments, the method can use extracted features to predict cardiotoxicity for physician evaluation. In certain embodiments, the method can use the extracted features to predict for cardiac clinical complications. In certain embodiments, the method can enable early cardiac toxicity prediction for cancer patients using standard-of-care FDG PET-CT imaging. In certain embodiments, the method can provide a cardiac management decision support tool using standard-of-care FDG PET-CT imaging. In certain embodiments, the method can enable the incorporation of the extracted features in radiation treatment planning (e.g., for patients whose management involves radiation) using standard-of-care FDG PET-CT imaging.

Traditional radiotherapy methods of evaluating, mitigating, and assessing for cardiotoxicity have focused on radiation doses to the heart (mean heart dose for example). A critical shortcoming of these dose-response models is that they determine population-based cardiotoxicity risk and often do not provide accurate or robust risk assessment for the majority of patients. Precise and personalized models for predicting cardiotoxicity are required to develop effective cardiotoxicity mitigation and intervention strategies. A method with great potential for improving the prediction of cardiotoxicity (and subsequently developing interventional strategies) centers on the idea of incorporating functional imaging into the assessment paradigm. Although FDG PET imaging is typically thought of as a way to image a tumor, it is also a standard imaging modality used to clinically assess the heart. Because FDG PET-CT scans are acquired as standard of care for lung cancer patients, the major advantage of using the cardiac Standardized Uptake Values (SUV) signal for cardiotoxicity assessment is that cardiac functional information can be acquired without requiring an additional scan for the patient. Based on the idea that FDG PET scans provide clinically valuable cardiac imaging information, our group recently investigated standard of care oncologic FDG PET-CT imaging to assess cardiac response to chemoradiation in lung cancer patients.

Cardiac FDG PET Radiomics measure metabolic activity and complements conventional perfusion imaging in the assessment of cardiac function (e.g., SPECT perfusion images or 82Rb/14N ammonia PET images for blood flow estimation and visual scoring using standard 17 segment left ventricle). Certain embodiments of the present disclosure analyze cardiac FDG PET images locally and/or globally using different texture features and

artificial intelligence (AI) and machine learning (ML) prediction. Radiomics can be more sensitive than current diagnostic methods in detecting subtle changes in the heart.

Aspects of the invention also includes a standalone vendor-neutral AI software application designed to predict cardiotoxicity in cancer patients using functional radiomics from 18F-FDG PET/CT scans. The application can operate on any system that is capable of running Python. In some implementations, the application can rely on significant libraries and framework. The software can be deployed on a local server or cloud environment and does not require integration with other software or hardware to control imaging equipment.

In some implementations, The application functions independently and can use PET/CT imaging data stored in the Digital Imaging and Communications in Medicine (DICOM) format, specifically for heart contour data in DICOM Structure Set (RTSTRUCT) format. The PET/CT and heart contour data enable the software to perform predictions without additional integration or dependencies. In some implementations, one of the preprocessing steps, automated heart contouring, can be performed to compare the results based on automated contours with those based on manual heart contours. This software primarily uses manual heart contours delineated by experienced medical physicists.

In some implementations, the software can integrate feature extraction and model building. A feature extraction workflow can simplify and scales complex data pipelines, enabling efficient and reproducible execution on local, cluster, or cloud computing environments. This workflow was specifically designed to process DICOM files, including PET/CT scans and associated heart contours, and to predict cardiac toxicity using functional radiomics. The process can begin by querying and retrieving DICOM images, converting them into the NRRD format or other 3D volume data format with physical space information through parallel processing, and then combining and filtering the outputs for consistency. The images were cropped to focus on the relevant regions, followed by feature extraction to identify significant radiomic features. The extracted features were then organized for the subsequent model-building process.

The organized features from radiomics tool can be inputs for the model-building process, which automates predictive model training for cardiotoxicity. This process utilizes a three-step radiomics pipeline— a feature selector, feature transformer, and classifier— integrated into a three-stage model-building approach: model Discovery, hyper-parameter optimization, and feature optimization. In some implementations, the pipeline analyzes functional radiomic features from 18F-FDG PET/CT scans to identify cardiac FDG uptake patterns indicative of potential cardiotoxicity. The three-stage training process can improve

the model's performance and interpretability. Pipeline optimization at each step can be performed using genetic programming-based methods, specifically the Tree-based Pipeline Optimization Tool (TPOT), which automates the process of pipeline configuration by evolving machine-learning pipelines through genetic programming techniques. TPOT optimizes the model by experimenting with different hyperparameters and pipeline configurations to achieve the best predictive performance.

In some implementations, at the model discovery, various machine learning algorithms can be used for each pipeline component. Example methods for a feature selector can include P-value (ANOVA F-statistic), family-wise error rate, percentile, low-variance feature removal, recursive feature elimination (RFE) with extra trees classifier, and/or the like. Example methods for a feature transformer can include binarization, independent component analysis (ICA), feature agglomeration, scaling (max absolute value, min-max values), normalization (L1, L2, max norm), kernel approximation, principal component analysis (PCA), polynomial features, RBF sampler, robust scaler, standard scaler, zero count, one hot encoder, and/or the like. Examples for a classifier can include naïve Bayesian (Bernoulli, multinomial), decision tree classifier, extra trees classifier, random forest classifier, gradient boosting classifier, XGBoost, K-nearest neighbors (KNN) classifier, linear SVM classifier, logistic regression, stochastic gradient descent (SGD), multi-layer perceptron (MLP), and/or the like.

At the model discovery, the hyper-parameter optimization can refine the selected model pipeline to enhance its performance and generalizability. This stage can involve systematically adjusting the hyperparameters of the selected algorithms to achieve optimal performance. The feature optimization can focus on selecting the most clinically relevant features. In this step, the final two components of the pipeline can be used for optimization and minimize the features through a dedicated feature selection method (e.g., recursive feature elimination and forward selection) applied to the features identified in the previous stages.

In some embodiments, the system as described herein can be trained using a robust dataset comprising pretreatment 18F-FDG PET/CT scans. In some implementations, the scans can be classified according to clinical cardiac guidelines as no uptake, diffuse uptake, or focal uptake. Feature reduction can be performed using the Wilcoxon test, hierarchical clustering, and recursive feature elimination, resulting in a final set of nine clinically

pertinent features. The training data can be divided into training (80%) and validation (20%) sets, and ten-fold cross-validation to assess the accuracy of the model.

Aspects of the invention can significantly impact clinical decision-making by providing a reliable, automated tool for predicting cardiotoxicity and subclinical cardiotoxicity, thereby improving patient outcomes and optimizing the use of cancer therapies (systemic chemotherapy, radiotherapy, immunotherapy, and other molecularly targeted agents) in cancer care.

Aspects of the present disclosure can be used for pre-treatment PET-CT scans and radiomics to predict for cardiac toxicity. Cardiac toxicity in lung cancer patients who have been treated with radiation therapy is a well-established side effect that decreases the survival rates of lung cancer patients. By using an AI radiomics model previously validated against clinician interpretation of FDG PET scans, obtaining data on cardiac toxicity can assist in generating a predictive risk model. The radiomics model as described herein can extract radiomics features associated with the heart in pretreatment PET scans, including the Standard Uptake Value (SUV), which is linked to overall survival. The purpose of this work was to utilize a radiomics model analyzing pretreatment FDG-PET scans in lung cancer patients to predict risk of cardiac toxicity. In some embodiments, the AI model can predict risk for cardiotoxicity after Feature Optimization and Hyperparameter Optimization using selected features in a training set. In some embodiments, the use of a radiomics model on pretreatment standard of care FDG-PET scans can predict the risk of future cardiac toxicity after radiation treatment, which can be used to help personalize treatment plans for patients at risk for cardiac toxicity and decrease its incidence.

Certain embodiments are best described in connection with the drawings. FIG. 1 illustrates an exemplary diagnostic PET/CT scan, including a signal 102 (e.g., cardiac uptake) of a target area 104. FIG. 2A illustrates signal 102a (e.g., uniform cardiac uptake, homogenous signal, etc.). FIG. 2B illustrates signal 102b (e.g., non-uniform cardiac uptake). FIG. 2C does not illustrate a detectable signal and illustrates an absence of cardiac uptake.

FIGS. 3A-3D illustrate different cardiac FDG PET/CT distributions indicative of different cardiac states. FIG. 3A-3D illustrate signals 102c, 102d, 102e, and 102f, respectively. FIG. 3 may indicate a normal cardiac state, while FIGS. 3A, 3B, and 3D may indicate abnormal cardiac function and sub-clinical cardiac complications.

FIG. 4 illustrates a schematic representation of radiomic features 116 used in connection with an AI model 118. Radiomic features 116 can be derived from a digital heart segmentation. Radiomic features can include shape features, including volume, subvolume,

high-intensity volume, low-intensity volume, texture pattern, and the like. In certain embodiments, a 2D feature is derived from a section with a large area of a diagnostic scan.

Referring now to FIG. 5, a system 100 for implementing methods described herein is illustrated. System 100 includes a scanner 106 configured to provide a diagnostic scan 108 (e.g., a computed tomography (CT) scanner, a positron emission tomography (PET) scanner, and a CT/PET scanner, a FDG CT/PET scanner, etc.), and a computer system 110. Computer system 110 is illustrated including a prediction pipeline 104 including AI/ML model (e.g., an artificial neural network) and a computer 112 (e.g., a personal computer device, a cloud computing device, etc.).

Scanner 106 is illustrated, providing a diagnostic scan 108 to computer system 110. Scanner 106 is communicatively coupled to the prediction pipeline 104. Diagnostic scan 108 can be processed by an Artificial Intelligence and Machine Learning model (e.g. U-Net architecture based model 114). The model architecture 114 can extract radiomics features implicitly (artificial neural network-based models), whereas typical radiomics-based models need explicit radiomics feature extraction process prior to the prediction. The prediction pipeline 104 is communicatively coupled to a computer 112. A cardiotoxicity prediction is determined based at least in part on the prediction pipeline 104 including AI/ML model (e.g., an artificial intelligence model).

Referring now to FIG. 6, a flow diagram of a method of the present disclosure is illustrated, in accordance with exemplary embodiments of the present disclosure. As is understood by those skilled in the art, certain steps included in the flow diagrams may be omitted; certain additional steps may be added; and the order of the steps may be altered from the order illustrated.

At Step 600, a diagnostic scan is conducted to generate a diagnostic image of a target area of a target patient.

At Step 602, one of more of the plurality of radiomic features are generated by a computer system, the computer system including an artificial intelligence model having been trained using another plurality of radiomic features of patients and a plurality of corresponding cardiotoxicities.

At Step 604, a predicted cardiotoxicity of the target patient is determined based at least in part on the artificial intelligence model

FIGS. 7-9 illustrate a schematic block diagrams of a) radiomics model building, b) radiomics model inference, and c) radiomics model refinement, respectively. A diagnostic

scan 120, feature database 122, clinical outcome database 124, and predicted outcome database 126 are illustrated throughout.

Referring specifically to FIG. 7, a diagnostic scan database 120 (e.g., a diagnostic PET/CT database) is provided. Such a database can be constructed using a plurality of diagnostic scan data (e.g., including diagnostic scan images). As illustrated, a manual or automatic heart segmentation can be done on data of the diagnostic scan database 120. Certain features include shape features, including volume, subvolume, high intensity volume, low intensity volume, texture pattern, and the like. can be extracted from the heart segmentation to construct a feature database 122. Such features can be provided to the prediction pipeline 104. Further, clinical outcomes (e.g., survival in months or years) can be provided to prediction pipeline 104 from a clinical outcome database 124. [

Fig 7 is general structure of Artificial Intelligence and Machine learning architecture model training. The input is a diagnostic scan 120, followed by heart segmentation, and radiomics feature extraction. The clinical outcome database 124 and stored radiomics feature database 122 can be used by the process of radiomics model building 104 for complete model training.

Fig 8 depicts a process to utilize the trained model via the architecture in Fig 7 for continuous model refinement. The input is a diagnostic scan, followed by heart segmentation and feature extraction, trained model prediction, and a cardio toxicity risk prediction for clinical use. The feature database 122 and predicted outcome database 126 can be used for continuous model refinement.

Fig 9 provides a detailed view of continuous model refinement as patient data is accumulated. The radiomics model can have a continuously updated feature database 122, clinical outcome database 124, and predicted outcome database 126. The updated feature database 122, clinical outcome database 124, and predicted outcome database 126 can be used for continuous radiomic model refinement.

FIG. 10 illustrates exemplary applications (e.g., treatments, changes in treatment protocols, etc.) of certain methods described herein. For example, when cardiotoxicity is determined to be low, a physician can proceed with cancer therapy and/or implement more aggressive trial combinations. In another example, when cardiotoxicity is determined to be moderate, a physician can send a patient to a cardiologist for increased surveillance and/or consider implement cardiac intervention. In another example, when cardiotoxicity is determined to be high, a physician can send a patient to cardiologist for increased surveillance, implement cardiac intervention, decrease chemo/immune/radio- therapy dose,

withhold chemo/immune/surgical therapy and/or alter radiotherapy treatment plan. Certain embodiments of the present disclosure can: function as a decision support tool for cardiac management; provides information on current subclinical cardiac disease; provide prediction of future cardiac problems; influence cancer treatment and management; and/or enable more targeted and personalized treatment plans. Certain embodiments of the present disclosure can: improve the accuracy of predicting cardiac clinical complications and cardiac function, provide a non-invasive diagnostic method, use standard of care imaging previously acquired for disease staging/assessment for a target patient, and enable earlier detection and management of cardiac complications and cardiac function.

Exemplary Study

Provided herein is an explanation of an exemplary study using certain methods of the present disclosure. The study developed a radiomics model to predict clinical cardiac assessment of standard of care FDG PET/CT scans. The study included 100 consecutive lung cancer patients treated with radiotherapy who underwent standard pre-treatment FDG-PET/CT staging scans. A clinician reviewed the PET/CT scans per clinical cardiac assessment guidelines and classified the cardiac uptake as: 0=uniform diffuse, 1=absent, 2=heterogeneous, with event rates of 20%, 44%, and 35%, respectively. The heart was delineated and 200 novel functional radiomics features were selected to classify cardiac FDG uptake patterns. The data can be divided into an 80% training set and a 20% test set to train and evaluate the classification models. Feature reduction was carried out using the Wilcoxon test (with Bonferroni adjusted $p<0.05$), hierarchical clustering, and Recursive Feature Elimination. Two automatic machine learning (AutoML) frameworks were used to determine classification models: a Random Forest Classifier (Tree-based Pipeline Optimization Tool, TPOT) and Linear Discriminant Analysis (AutoSklearn). 10-fold cross validation was carried out for training and the accuracy of the ability of the models to predict for clinical cardiac assessment is reported.

Fifty-one (51) independent radiomics features were reduced to 3 clinically pertinent features (PET 2D Skewness, PET Grey Level Co-occurrence Matrix Correlation, and PET Median) using feature reduction techniques. The model selected by TPOT showed 89.8% predictive accuracy in the cross validation of the training set and 85% predictive accuracy on the test set. The model selected by AutoSklearn showed 89.7% predictive accuracy in the cross validation of the training set and 80% predictive accuracy on the test set.

The study described developed and evaluated functional cardiac radiomic features from standard of care FDG PET/CT scans with the data showing good predictive accuracy with clinical imaging evaluation. The study illustrates the use of exemplary embodiments (e.g., automated methods) which can be used to provide functional cardiac information using standard of care imaging that can be used as an imaging biomarker for early clinical toxicity prediction for lung cancer patients.

EXAMPLES

EXAMPLE 1 – Novel Functional Imaging Radiomic Signatures for Cardiotoxicity in Lung Cancer Patients

Provided herein is a development of functional imaging radiomic signatures for the early prediction of cardiotoxicity in patients with lung cancer. Patients with lung cancer treated with radiotherapy are at significant risk of developing cardiac toxicity. Studies have highlighted the clinical impact of radiation dose to the heart for patients with lung cancer receiving radiation therapy. There is a link between cardiac dose and overall survival (OS), cardiotoxicity, and cardiac mortality. Patients who receive higher radiation doses to the heart are likely to have decreased survival, increased cardiac events, and increased rates of death due to cardiac events. In addition to radiotherapy, lung cancer patients are treated with chemotherapy, immunotherapy, and surgery. Chemotherapy and molecular-targeted therapies have been shown to increase the likelihood of cardiotoxicity. Although the addition of immunotherapy to chemoradiation has improved survival, a tradeoff exists between disease control and side effects; in particular, the rate of cardiotoxicity increases with the addition of immunotherapy. For patients with lung cancer undergoing treatment, the rates of clinically significant cardiotoxicity can range from 20% to 30%. Cardiotoxicity, a dangerous and potentially life-threatening side effect, is a substantial hurdle in the treatment of lung cancer. The risk of cardiotoxicity limits the use of combinations of aggressive therapies that can be evaluated in clinical trials.

Methods described herein can evaluate the pre- to post-treatment changes in the cardiac FDG PET signal using SUV, which can find two distinct phenotypes: patients who had a pre- to post-treatment increase in cardiac SUV and those who had a pre- to post-treatment decrease in cardiac SUV (FIG. 3). SUV changes in the heart can be predictive of OS on multivariate analysis: patients who had an increase in cardiac SUV lived significantly longer than those who had a decrease in cardiac SUV (FIG. 11). The results showing that

cardiac SUV changes are predictive of OS were confirmed in 2 separate lung cancer cohorts, reproduced in an esophageal cancer cohort.

There is great potential to improve the predictive ability of FDG PET-based functional imaging models using radiomics-based methods and advanced deep learning (DL) approaches. Radiomics can extract a large number of features from imaging data and can provide imaging information beyond basic mean and maximum metrics. Recent advancements in DL architectures have enabled the emergence of multi-label learning methods that allow for the inclusion of multi-omics data and the joint prediction of multiple endpoints (e.g., OS and cardiotoxicity). FDG PET cardiac imaging combined with novel radiomics and DL methods can repurpose standard of care imaging to provide an early and accurate identification of patients at increased risk of cardiotoxicity.

FDG PET imaging-based models for cardiotoxicity prediction can significantly improve outcomes in patients with lung cancer. In some implementations, methods described herein can include building an extensive patient database for evaluation of PET imaging and cardiotoxicity and to develop novel radiomic signatures and DL models based on FDG PET imaging for the prediction of early cardiotoxicity In some embodiments, the database described herein can evaluate robust functional imaging-based cardiotoxicity models and develop novel, PET-based models that can provide early identification of patients who are at risk of developing cardiac toxicity. The models can use standard of care imaging (FDG PET-CT), to identify patients at risk for developing cardiotoxicity. The developed models can be used for cardiotoxicity mitigation strategies including altered functional imaging-based clinical decision support tools, early vigilance, cardiac toxicity interventions, and radiation planning strategies to reduce risk of cardiotoxicity.

Innovation

The methods described herein can present several key innovations that can reduce the risk of cardiotoxicity in lung cancer patients treated with radiotherapy. FDG PET-CT scans are acquired as standard of care for lung cancer patients to detect disease, characterize the response to treatment, and help delineate the gross tumor volume. The methods described herein can include generating functional imaging cardiac prediction models using imaging information acquired as part of the standard of oncologic care. A significant innovation in the novel methods is that cardiac imaging information can be obtained by repurposing standard of care FDG PET-CT scans thereby not burdening the patient with an extra imaging procedure.

Previous models developed for cardiotoxicity can be primitive and based on radiation doses to the heart along with baseline cardiac factors. Work evaluating the cardiac signal from FDG PET scans has relied on basic PET metrics such as mean and maximum SUV. The most accurate functional imaging-based predictive models likely involve a diverse set of covariates, and the accuracy of these models can be significantly improved with advanced DL approaches and functional radiomics metrics. An important innovation here is that it includes a wide array of functional imaging advancements. The investigated cardiac FDG PET radiomics can include intensity-volume histogram metrics, texture features, shape features, wavelet features, and learned features by DL. Radiomics metrics can be evaluated for the entire heart, and cardiac sub-structures found to be critical in predicting for cardiac toxicity. In addition to FDG PET radiomics features, comprehensive covariates can be evaluated, including patient, clinical, baseline cardiac, and radiation dose parameters. A comprehensive cardiac toxicity model based on functional radiomics and pertinent clinical parameters has yet to be developed.

In some implementation, the database as described herein can include a dataset that includes FDG PET scans, cardiac toxicity data, clinical and patient data, and radiotherapy data. The collection of FDG PET scans can include Digital Imaging and Communications in Medicine (DICOM) data and important scan metadata including scanner accreditation and type, patient glucose level, and SUV calibration information. Patient and clinical factors can include age, gender, pre-existing cardiac conditions, race, ethnicity, and socioeconomic status. The collected radiotherapy DICOM data can include the planning CT scan, structure set, dose distribution, and radiotherapy plan. Building a large and robust database can enable sufficient statistical power, allow us to address model over-fitting challenges, facilitate evaluation of the impact of PET scanner parameters, and enable for the exploration of sub-types of cardiac toxicity.

Preliminary Data

Radiation therapy remains one of the primary modes of treatment for patients with lung cancer, with 60% to 80% of patients receiving radiotherapy as part of their disease management. Lung cancer patients treated with radiotherapy can receive high radiation doses to the heart. A significant body of lung cancer literature has highlighted the clinical impact of radiation dose on the heart and the associated risk of cardiotoxicity. There is a link between cardiac dose and OS, cardiotoxicity, and cardiac mortality. Patients who receive higher

radiation doses to the heart are likely not to live as long, have an increased probability of cardiac events, and experience death due to cardiac events.

As part of the standard management for patients with lung cancer, radiotherapy is often combined with immunotherapy, chemotherapy, or targeted molecular therapy, which all compound the risk of cardiotoxicity. Functional imaging can be incorporated into cardiac toxicity models and has great potential to improve robustness and accuracy in predicting cardiotoxicity. In some cases, functional imaging as described herein can predict which patients can develop pulmonary side effects when compared to dose metrics alone.

Multiple imaging modalities can be used to image the heart including echocardiograms, cardiac Magnetic Resonance Imaging (MRI), CT angiography, nuclear medicine including Single-photon emission computed tomography (SPECT), and PET imaging. PET imaging has excellent diagnostic accuracy for imaging myocarditis, inflammation, and coronary disease. PET imaging has been shown to have high diagnostic accuracy in screening for myocarditis and cardiotoxicity. FDG PET imaging can be used to image the heart for myocardial viability and cardiac inflammation (typically used to diagnose cardiac sarcoidosis).

FIG. 12 shows a representative patient from our institution with a cardiac FDG PET-CT demonstrating abnormal uptake in the heart, indicating cardiac sarcoidosis. FDG PET scans have limited use in diagnostic heart imaging because of their high cost and increased radiation exposure. However, in the oncology domain, the impact of high cost and radiation exposure can be limited, as the scans are acquired as a standard of care.

In the oncology paradigm, FDG PET can be typically considered an imaging modality for imaging a tumor. Based on the idea that the acquisition protocols for cardiac inflammation FDG PET scans are identical to the parameters of oncologic FDG PET scans, FDG PET scans have been used to evaluate radiation normal tissue damage in other organs, and the standard that FDG PET imaging can detect inflammation (which is an important process for normal tissue damage), there is utility of oncologic FDG PET-CT scans in assessing the cardiac response to radiation. By contouring the heart in the pre- and post-treatment PET-CT scans and assessed the SUV changes in the heart, it can be found there can be a dose-response (the SUV in the heart changed as a function of dose) and that the cardiac SUV changes were predictive of OS on multivariate Cox proportional hazards survival analysis. In some implementations, cardiac SUV metrics can predict OS with a hazard ratio = 0.541 (95% confidence interval of 0.312 to 0.937, $p<0.028$) and that there can be a significant

difference in survival curves for patients who showed a decrease versus increase in post-treatment cardiac SUV when compared to pre-treatment cardiac SUV (as shown in FIG. 11).

FIG. 14A demonstrates how the FDG PET signal in the heart is indicative of radiation-induced pericarditis after chemoradiation and FIG. 14B demonstrates how the FDG PET signal in the heart is indicative of cardiomyopathy after chemoradiation. In some implementations, there is precedent for using FDG-PET imaging as an imaging biomarker in radiotherapy for other normal tissues including the parotid for head and neck cancer and lung tissue for lung cancer. For instance, FDG-PET imaging can show significant SUV changes in normal lung in the irradiated region signifying an inflammatory response that subsequently predicted for pneumonitis. For head and neck treatments, FDG-PET imaging can show decreasing FDG uptake in the parotid gland as a function of dose. FDG-PET imaging can show that SUV features significantly improved prediction of xerostomia.

In cardiac imaging and radiotherapy, a variety of imaging biomarkers have been used to image the heart including echocardiograms, cardiac MRI, and SPECT. The significant advantage of FDG PET scans can be that the data are acquired as part of the standard of care for oncologic imaging, thereby sparing the patients from an extra imaging procedure, reducing the cost, and reducing the imaging radiation exposure. Taken together, the preliminary data, FDG PET cardiac imaging clinical guidelines, and the precedent of using FDG PET imaging to characterize toxicity for other normal tissues, underline great potential for using standard of care oncologic FDG PET-CT scans as an early predictor of cardiotoxicity. An early cardiac toxicity prediction model can provide a decision support tool and enable early intervention, including prompt cardiology evaluation and modification of the radiation treatment plan.

Cardiac radiomics and deep learning methods for cardiotoxicity prediction: Radiomics can be a computationally intensive method that extracts a large number of features from imaging data and can provide information that is not visible to the human eye. FDG PET-CT radiomics can be used to evaluate lung cancer tumor shape, size, and texture features to predict histology and clinical outcomes. In the radiology domain, cardiac radiomics and deep learning methods can be used for cardiotoxicity prediction and to evaluate the ability of echocardiogram, MRI, and SPECT imaging to predict cardiovascular.

Approach

DICOM imaging and radiotherapy data can be collected and a platform that allows for the anonymization and aggregation of DICOM data can be used. A >400-patient multi-institutional database can be used and deployed for functional imaging and ML studies. A

database can store a 1000-patient multi-institutional dataset using patient data in which eligible patients can include patients with stage III lung cancer, treated with radiotherapy, who have pre-treatment and post-treatment standard staging and follow-up FDG PET-CT scans, and who have ≥4 years of follow-up. Patients with non-small cell and small-cell lung cancer histology can be included in the database. Patients with early-stage lung cancer are not included in the database because they receive lower doses to the heart and are at lower risk for cardiotoxicity when compared to advanced-stage lung cancer patients.

Collected data can be divided into 5 categories: patient, clinical, cardiotoxicity, radiotherapy, and FDG PET-CT imaging (as shown in FIG. 13). Patient factors can include age, gender, performance status and social determinants of health factors (race, ethnicity, and socioeconomic status). Clinical factors can include disease stage, histology, existing comorbidities, and treatment modalities the patient was treated with (chemotherapy, immunotherapy, molecular therapy, and surgery). Collected baseline cardiotoxicity data can include CTCAE-graded baseline cardiac conditions, electrocardiographic findings, echocardiographic findings (diastolic parameters, systolic parameters, left atrial volume index, valvular abnormalities, and presence/absence of pulmonary hypertension). Follow-up cardiotoxicity data can be collected for at least 4 years (and longer if data is available) and can include CTCAE-based cardiotoxicity as well as explicit grading for symptomatic pericardial effusion, myocardial infarction, unstable angina, pericarditis, arrhythmia (atrial and ventricular), and heart failure. Radiotherapy data can include DICOM data for the planning CT, structure set, dose, and RTPlan data. FDG PET-CT data can consist of the DICOM attenuation-corrected PET scans, accompanying CT scans, and meta data including scanner type and model, accreditation, calibration information, and the blood glucose level of the patient at the time of the scan. Pre- and post-radiotherapy FDG PET-CT scans can be collected.

As described herein, large multi-institutional database consisting of patient, clinical, cardiotoxicity, radiotherapy, and functional imaging data can provide both functional imaging and cardiotoxicity data. It can also provide a unique opportunity to develop cardiotoxicity models that enable independent validation using multi-institutional data.

As described herein, a pre-treatment FDG PET cardiac radiomics model can be developed for early prediction of cardiotoxicity. This pre-treatment cardiotoxicity prediction model can be used to guide the development of personalized radiotherapy treatment plans and aid in pre-treatment clinical decisions. FIG. 14 shows pre-treatment factors that can be evaluated in the pre-treatment FDG PET cardiac radiomics model. Before developing

functional imaging-based models, a baseline for cardiotoxicity can be established using factors that are known to predict cardiac toxicity. Baseline model parameters can include patient, clinical, and treatment-related factors. Examples of patient factors include age, smoking status, weight, blood pressure, and performance status. The cardiotoxicity model can explicitly evaluate sex as a biological variable and assess whether gender plays a role in developing cardiotoxicity. Clinical factors assessed can include pre-existing cardiac conditions. Treatment-related factors include the presence and type of surgery, immunotherapy, chemotherapy, and molecular therapy administered to the patient. Social determinants of health, including being a racial minority and having a low median household income, have been shown to impact an individual's risk of having cardiovascular disease. Therefore, the developed models can evaluate social determinants of health factors as a predictor of cardiac toxicity. The models an be assessed using a primary endpoint of ≥ grade 2 CTCAE cardiotoxicity. Additional endpoints evaluated can be OS, cardiac mortality, and sub-types of cardiac toxicity including myocardial infarction, heart failure, new coronary artery disease, conduction event abnormalities, arrhythmias, and pericardial effusion.

In some implementations, the development of functional cardiac PET radiomics can derive novel radiomics-based features from the pre-treatment cardiac PET signal. The heart and cardiac structures can be contoured, and SUV values can be assessed. Appropriate pre-processing of the PET images can be applied, including resampling and SUV normalization strategies. The normalization strategies can be designed to mitigate the uncertainties associated with obtaining SUV values on different scanners. Standard PET-based metrics can be evaluated including SUV mean, SUV max, and SUV. A comprehensive set of more than 1000 radiomics features can be extracted which can include first-order statistics, texture features such as gray level co-occurrence matrix (GLCM), gray level size zone matrix, gray level run length matrix, neighboring gray-tone difference matrix, gray level dependence matrix (GLDM), and 2D and 3D shape features. Filtering methods can be used to derive additional features including Gradient, Logarithm, SquareRoot, and Wavelet features.

The baseline and cardiac radiomics models can be further built by evaluating dose and dosiomic metrics for the prediction of cardiotoxicity. Standard dose metrics evaluated can include mean heart dose and the volume of heart receiving ≥5 Gy, ≥30 Gy, ≥40 Gy, and ≥60 Gy. Doses can be evaluated in cardiac sub-structures, including the anterior descending coronary artery and the left ventricle. A radiomics approach applied to the radiation dose distribution, referred to as dosiomics, canextract spatial and texture features from the dose distribution. Dosiomics can provide data beyond standard dose metrics and has been used to

improve prediction of pulmonary toxicity, disease cure rates, and/or cardiotoxicity. Evaluated dosiomics features can include dose GLCM, dose gray level size zone matrix, and 2D and 3D dose shape features.

In some implementations, the final version of the pre-treatment cardiotoxicity model can include both dose and PET-based functional imaging metrics. In some implementations, combinations of PET-based imaging metrics and dose metrics can be used to assess whether dose-function metrics can improve prediction of cardiotoxicity. Novel dose-function evaluations can include dose in higher/lower functioning portions of the heart, dose-function histogram metrics, and nonlinear combinations of dose and PET-based cardiac function. The developed cardiac dose and dose-function metrics can be assessed for their ability to predict ≥ grade 2 cardiotoxicity.

Because there is expected to be a considerable number of PET-radiomics, DL, and delta-radiomics features), as well as clinical, dose, and patient factors, feature reduction methods can be applied to ensure model over-fitting does not occur. For instance, intraclass correlation coefficients, the Wilcoxon-based predictor, and hierarchical clustering in a step-wise fashion can be used to reduce the number of features. The number of features can be optimized by applying the Recursive Feature Elimination, Sequential Forward Selection, and implicit feature selection through model building (e.g. LASSO, ensemble learning, and DL). The optimized model can be evaluated by time-dependent receiver operating characteristic area under the curve, accuracy, precision, recall and f1-score.

The cardiotoxicity models as described herein can be based on functional radiomics, clinical metrics, dose, and dose-function metrics that combine functional imaging and dose. The functional radiomics model can enable early, pre-treatment cardiac toxicity risk prediction using standard of care imaging. Pre-treatment toxicity prediction models can enable modifying the radiation plan including fractionation, allowed dose to the heart, or target volume definition or sending the patient to a cardioncologist for early cardiac assessment.

EXAMPLE 2 – Novel Functional Radiomics for Prediction of Cardiac Positron Emission Tomography Avidity in Lung Cancer Radiotherapy

Methods

Radiomics Feature Extraction

FDG-PET/CT radiomics can be used to analyze FDG uptake patterns of the heart. The heart can be delineated on the CT from the FDG-PET/CT following RTOG heart atlas. In

addition, to evaluate feature robustness and a completely automated solution, an AI auto contouring tool can be used to segment the heart. Once the heart was contoured on the CT from the FDG-PET/CT, the contours can be transferred to the corresponding PET images. The heart contours can be visually reviewed on both the CT and PET images to confirm there was no misalignment of the images. Radiomics features can be extracted from the PET image within the heart contour, which included first-order statistics, texture features such as gray level co-occurrence matrix (GLCM), gray level size zone matrix, gray level run length matrix, neighboring gray-tone difference matrix, gray level dependence matrix (GLDM), and 2D and 3D shape features.

Feature Selection

The training data can be divided into an 80% training set and a 20% validation set to train and validate the classification models. Before building classification models, intraclass correlation coefficient (ICC) can be used between features extracted by manual and automated segmentation to filter out nonrobust features when the ICC is <0.9. For the remaining features, the predictive capability of each feature can be assessed using the Wilcoxon test and identified good predictors on the basis of a Bonferroni-adjusted P value of <.05. Highly correlated features can be removed through hierarchical clustering to minimize collinearity.

Model Building and Evaluation

A tree-based pipeline optimization tool can be used for automating machine learning framework to discover preliminary classification models by automating the machine learning pipeline and using genetic programming, an optimization technique, to build the best program by mimicking the natural selection process of evolution. Model can be selected on the basis of the highest accuracy score on the validation set through the three-step prediction pipeline optimization using the framework, which include (1) model discovery, (2) hyperparameter optimization, and (3) feature optimization.

Results

Radiomics Feature Selection and Model Building

After hyperparameter optimization, the pipeline can be updated as shown in the second row of FIG. 16. On the basis of the discovered prediction pipeline, the number of features can be optimized such that nine features can be selected as the best that maintained

performance while reducing the number of features. The optimized pipeline is shown in the last row in FIG. 16.

The methods described herein can evaluate a novel radiomics model to predict cardiac FDG uptake patterns using standard-of-care pretreatment PET/CT staging scans for patients with lung cancer. In some implementations, The novelty of the present disclosure is that a large patient data set can be used to develop a robust, automated radiomics model to predict cardiac clinical interpretations of FDG PET scans with reasonable accuracy as validated on independent cohorts. If further validated, this radiomics model, when combined with another patient, clinical, and treatment parameters, can provide an automated method to use the standard-of-care staging FDG PET/CT scans to predict both existing cardiac conditions and provide an early functional biomarker to identify patients at risk of developing cardiac complications after radiotherapy.

EQUIVALENTS

Although preferred embodiments of the invention have been described using specific terms, such description is for illustrative purposes only, and it is to be understood that changes and variations may be made without departing from the spirit or scope of the following claims.

INCORPORATION BY REFERENCE

The entire contents of all patents, published patent applications, and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

CLAIMS

1. A method comprising:

a) conducting a diagnostic scan to generate a diagnostic image of a target area of a target patient, the diagnostic image including a plurality of radiomic features of the target area;

b) providing one of more of the plurality of radiomic features to a computer system, the computer system including an artificial intelligence model having been trained using another plurality of radiomic features of patients and a plurality of corresponding cardiotoxicities; and

c) determining a predicted cardiotoxicity of the target patient based at least in part on the artificial intelligence model.

2. The method of claim 1, wherein the radiomic features include one or more selected from the group consisting of: shape, intensity features, and texture.

3. The method of claim 1 wherein the diagnostic scan is a PET/CT scan.

4. The method of claim 1 wherein the target area is selected from the group consisting of: a targeted tumor and tissue surrounding a cancerous region, the target area including a cardiac area.

5. The method of claim 1 wherein step a) generates a single diagnostic image.

6. The method of claim 1 wherein step a) generates a plurality of diagnostic images.

7. The method of claim 1 wherein the one or more diagnostic images are three-dimensional images.

8. The method of claim 1, further comprising: providing a treatment plan based at least in part on the predicted cardiotoxicity.

9. A system for implementing the methods of any of claims 1-8 comprising:

a computer system including an artificial intelligence model and a computer.

10. The system of claim 9, further comprising:

a scanner configured to provide a diagnostic scan, the scanner being selected from the group consisting of: a computed tomography (CT) scanner, a positron emission tomography (PET) scanner, and a CT/PET scanner.

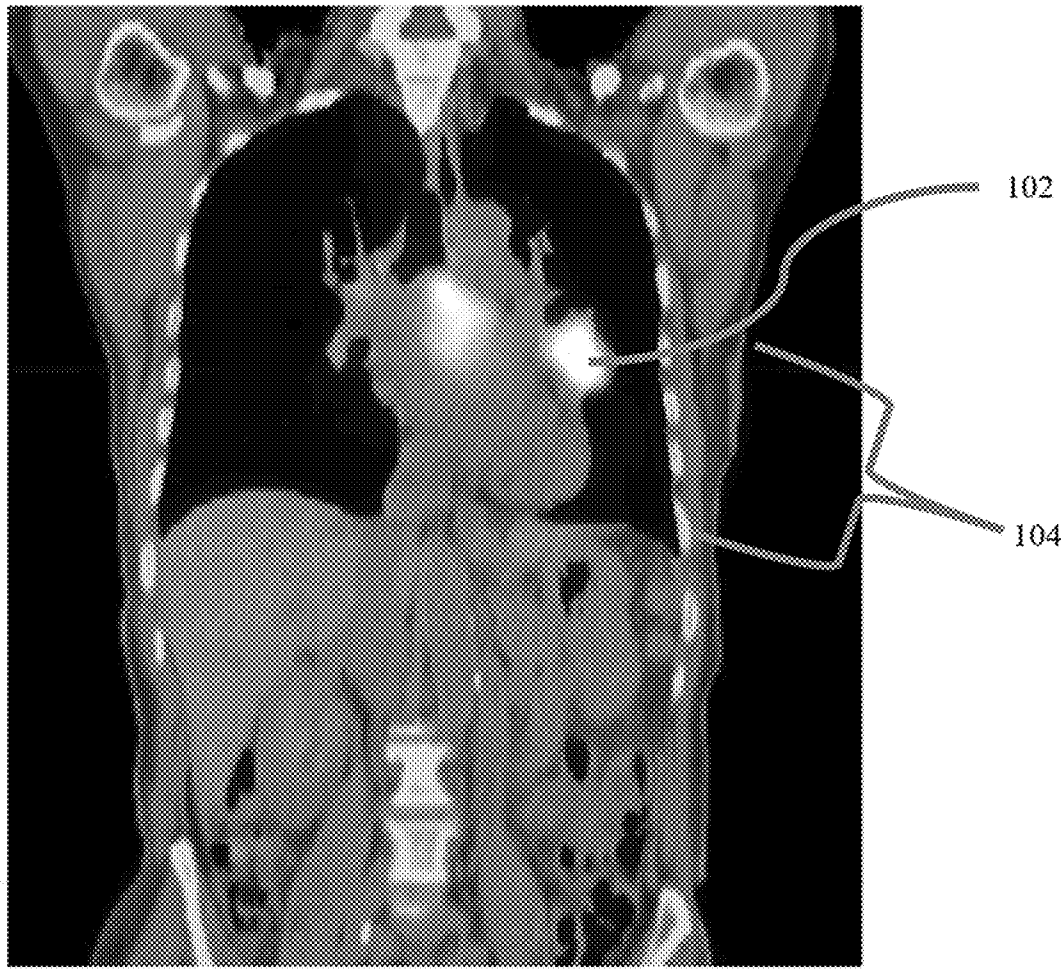

FIG. 1

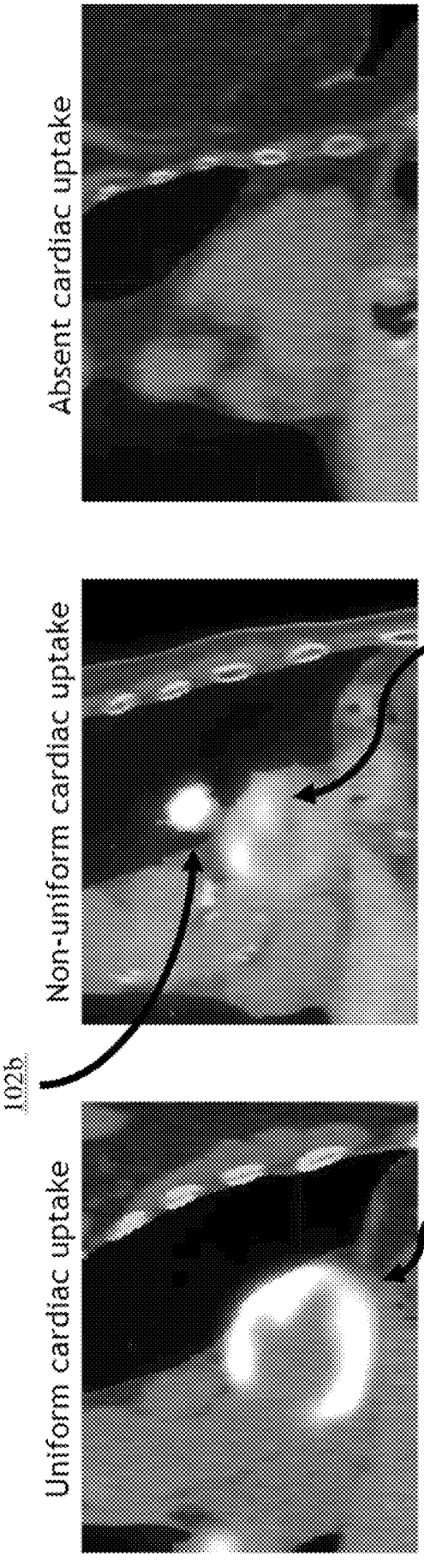

FIG. 2A

FIG. 2B

FIG. 2C

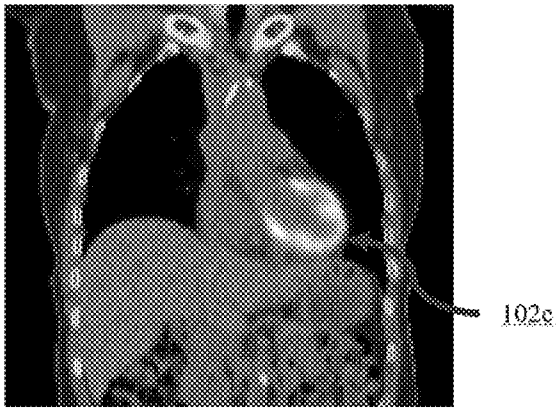

FIG. 3A

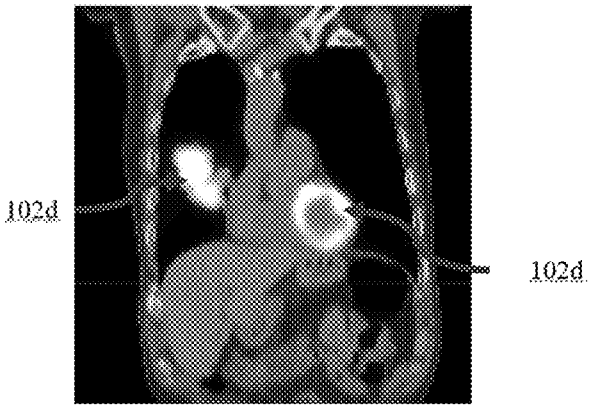

FIG. 3B

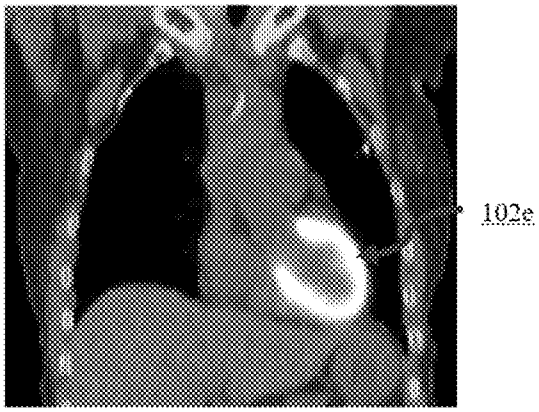

FIG. 3C

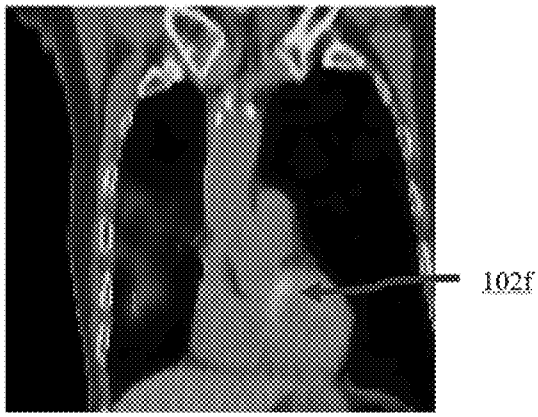

FIG. 3D

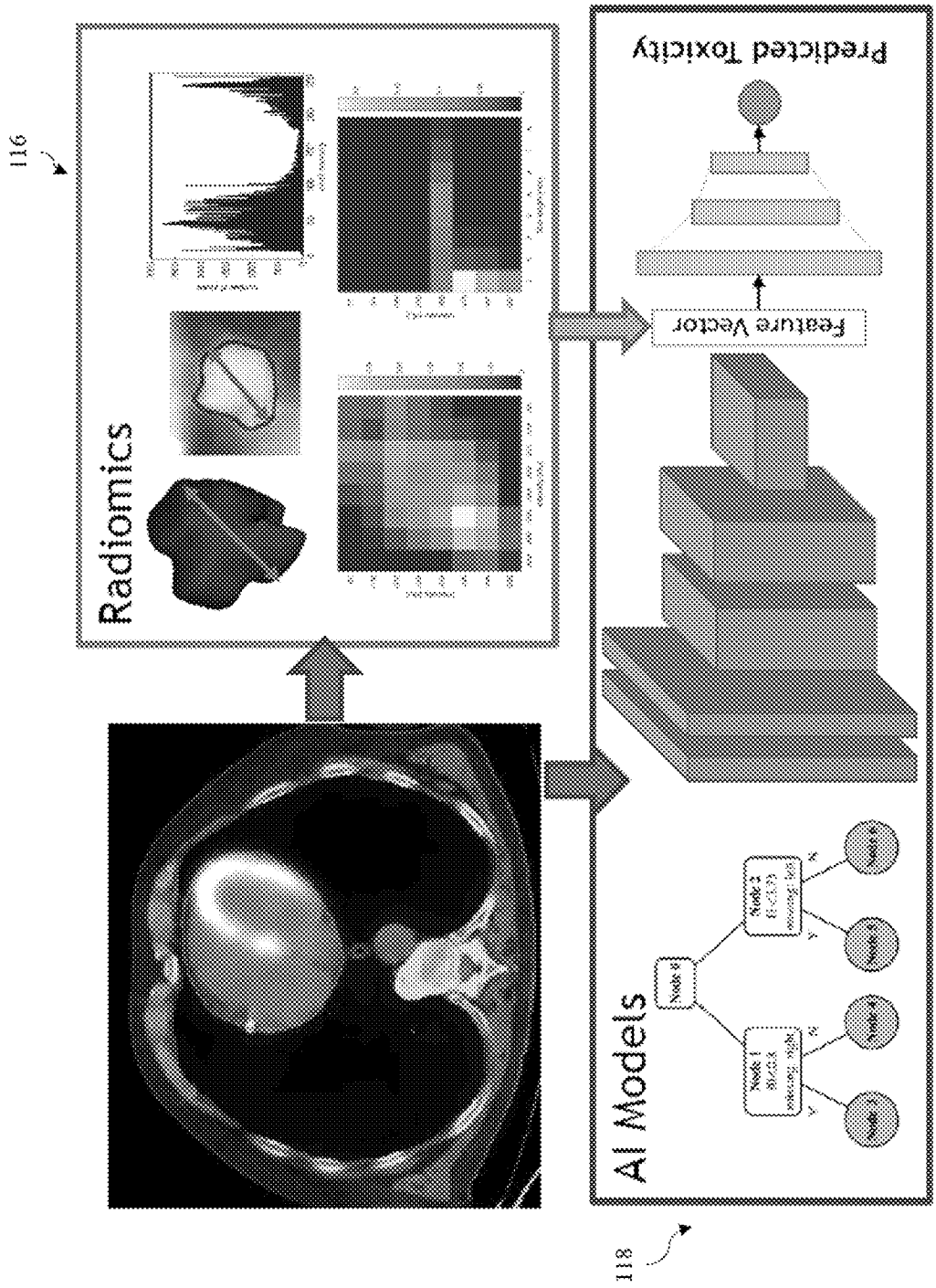
116
Radiomics
Predicted Toxicity
Feature Vector
AI Models
118

FIG. 4

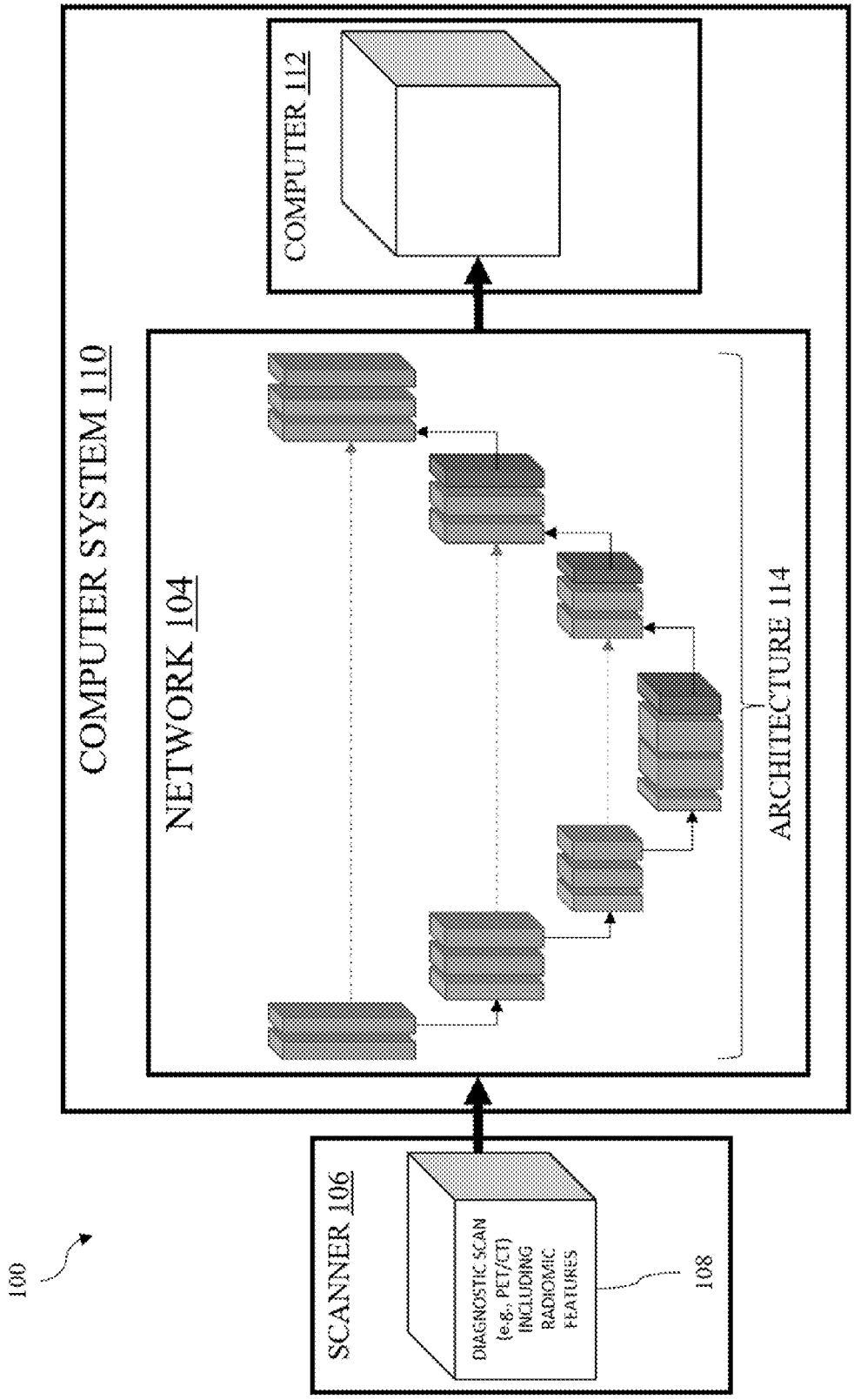
100
SCANNER 106
DIAGNOSTIC SCAN (e.g., PET/CT) INCLUDING RADIOMIC FEATURES
108
COMPUTER SYSTEM 110
NETWORK 104
ARCHITECTURE 114
COMPUTER 112

FIG. 5

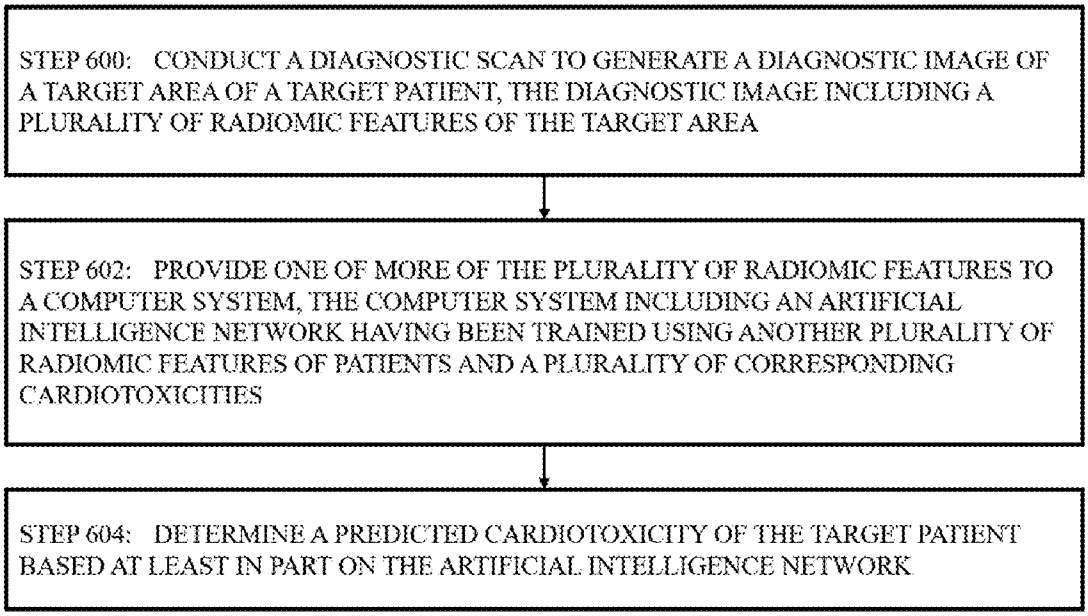
STEP 600: CONDUCT A DIAGNOSTIC SCAN TO GENERATE A DIAGNOSTIC IMAGE OF A TARGET AREA OF A TARGET PATIENT, THE DIAGNOSTIC IMAGE INCLUDING A PLURALITY OF RADIOMIC FEATURES OF THE TARGET AREA
STEP 602: PROVIDE ONE OF MORE OF THE PLURALITY OF RADIOMIC FEATURES TO A COMPUTER SYSTEM, THE COMPUTER SYSTEM INCLUDING AN ARTIFICIAL INTELLIGENCE NETWORK HAVING BEEN TRAINED USING ANOTHER PLURALITY OF RADIOMIC FEATURES OF PATIENTS AND A PLURALITY OF CORRESPONDING CARDIOTOXICITIES
STEP 604: DETERMINE A PREDICTED CARDIOTOXICITY OF THE TARGET PATIENT BASED AT LEAST IN PART ON THE ARTIFICIAL INTELLIGENCE NETWORK

FIG. 6

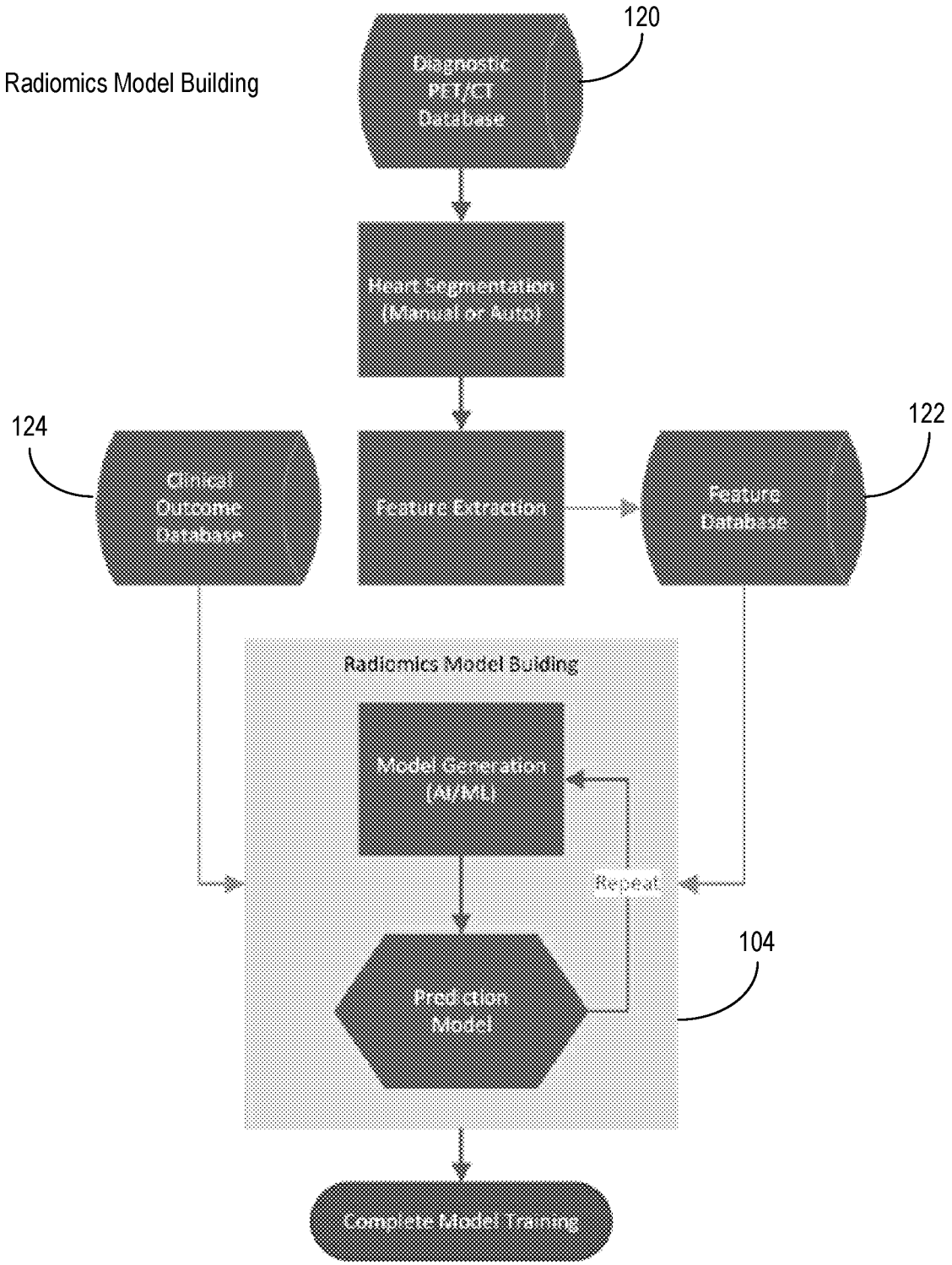
Radiomics Model Building
120
Diagnostic PET/CT Database
Heart Segmentation (Manual or Auto)
124
Clinical Outcome Database
Feature Extraction
122
Feature Database
Radiomics Model Building
Model Generation (AI/ML)
Repeat
104
Prediction Model
Complete Model Training

FIG. 7

Radiomics Model Inference

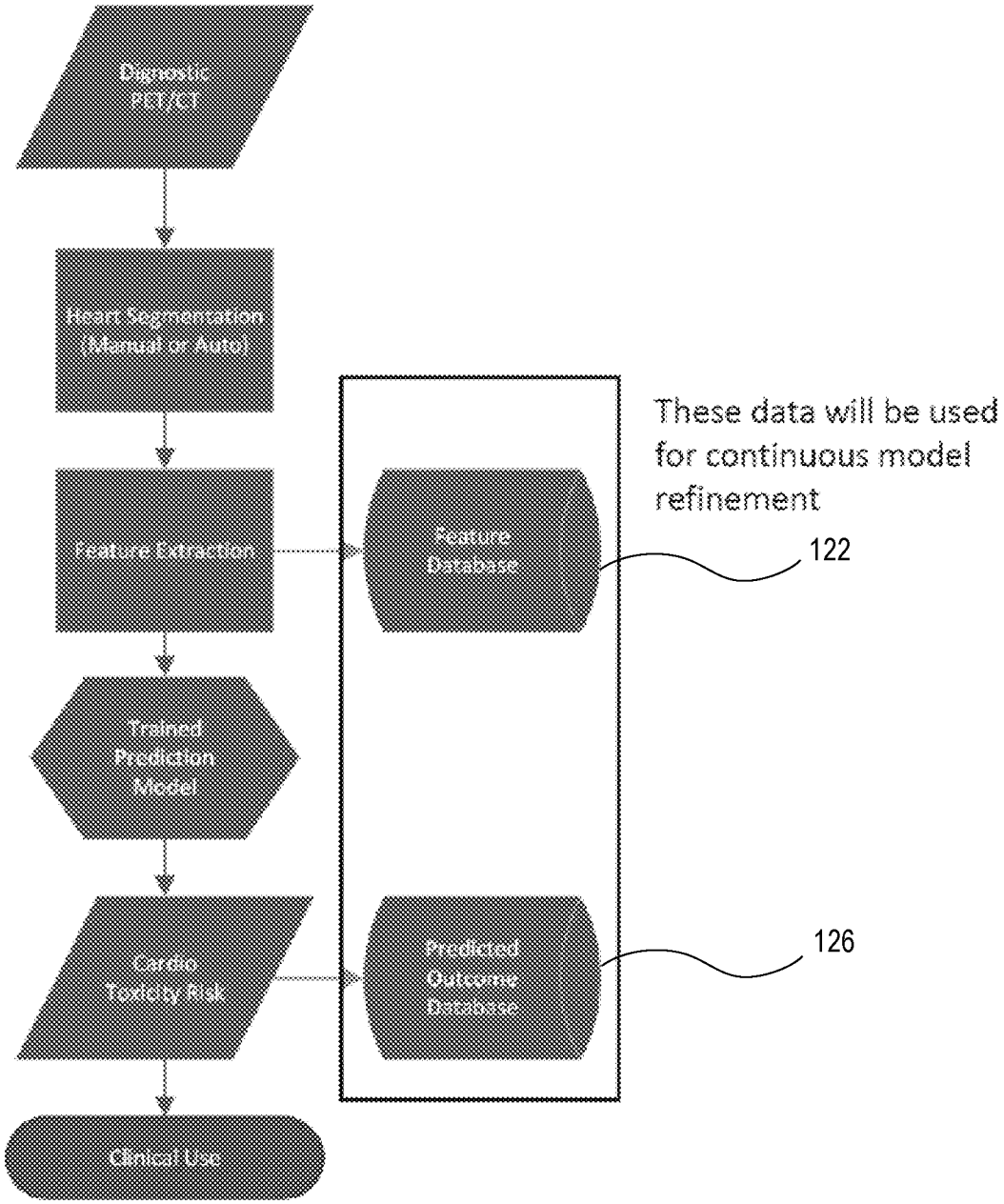

FIG. 8

Radiomics Model Refinement

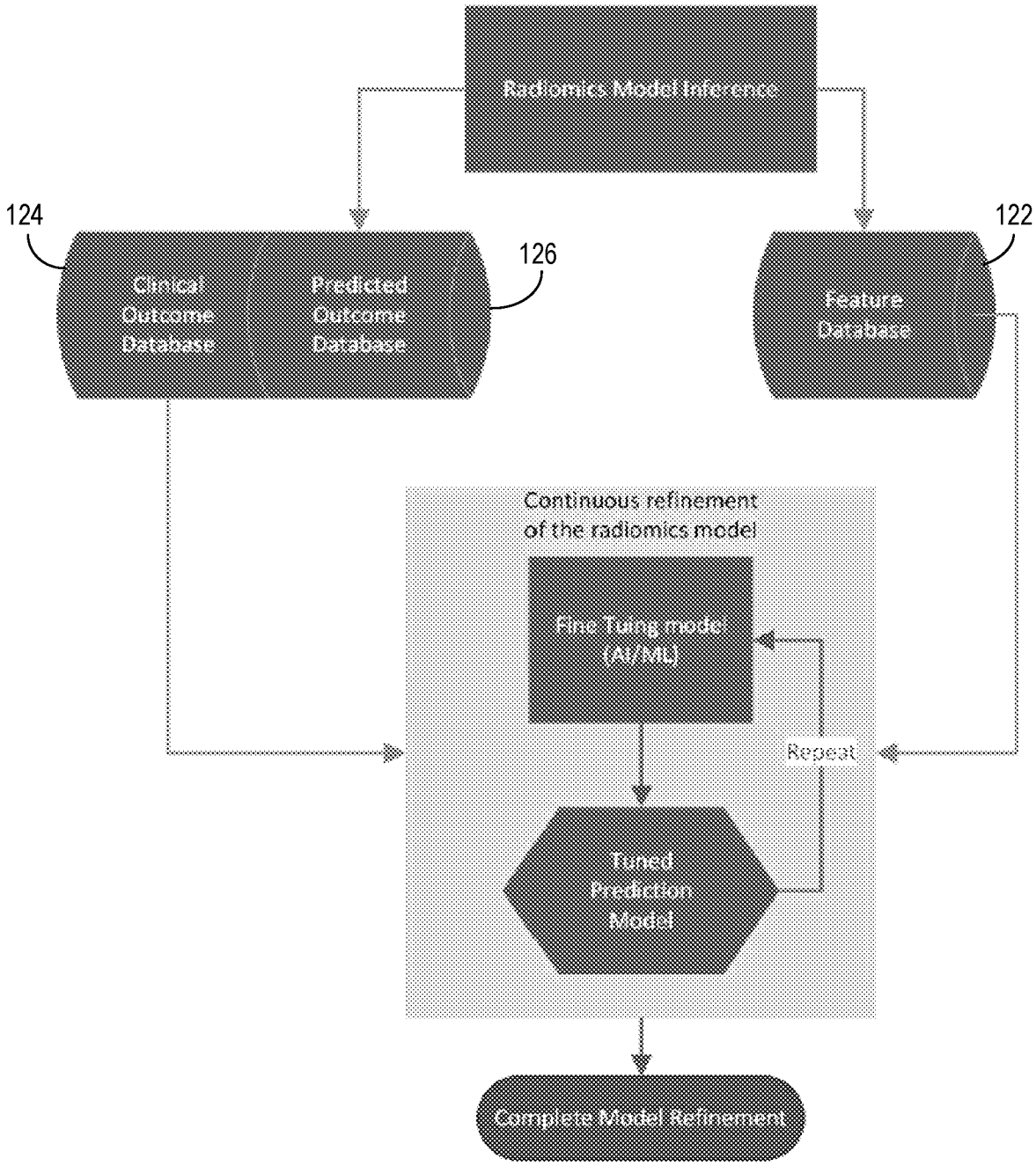

FIG. 9

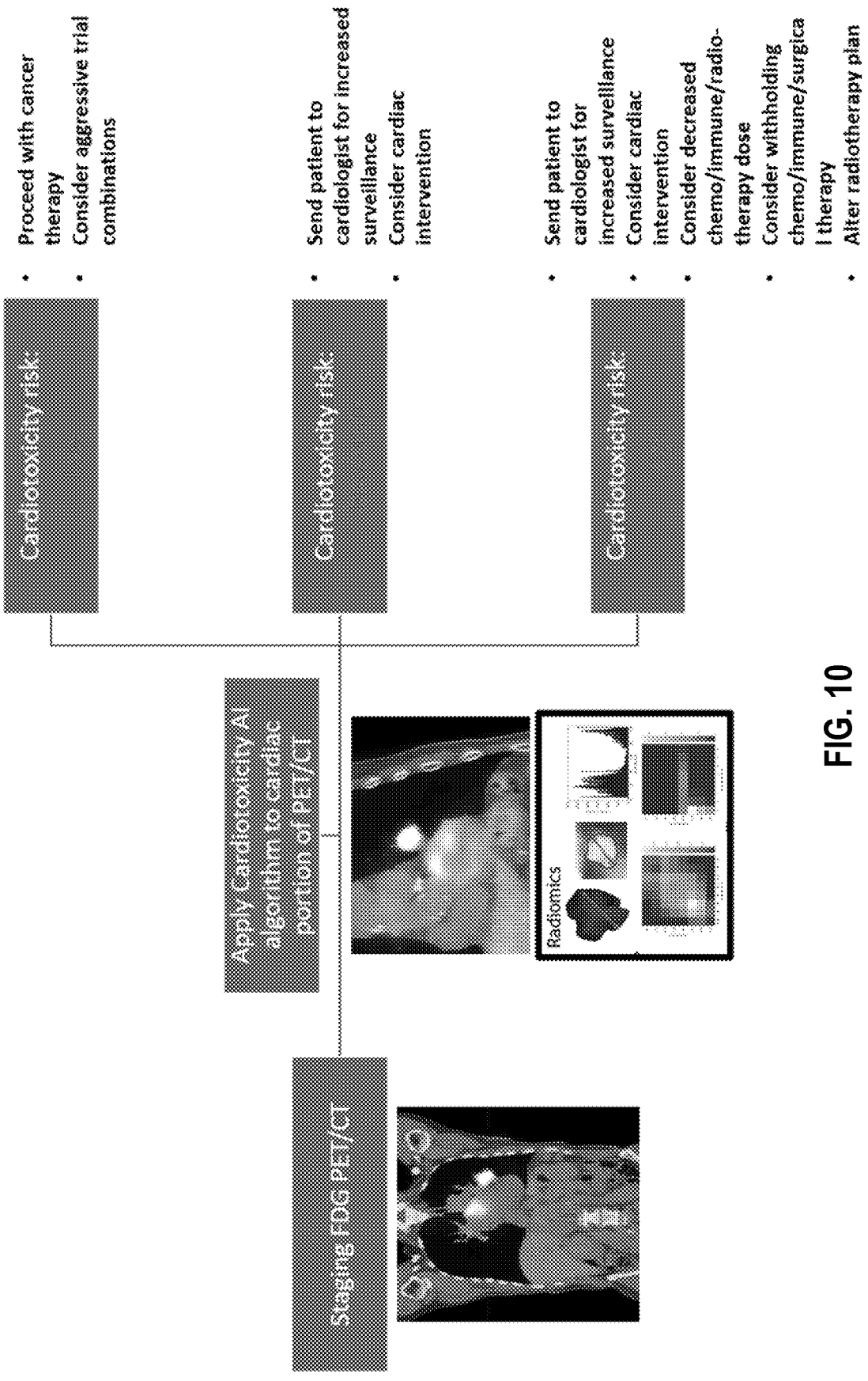
Staging FDG PET/CT
Apply Cardiotoxicity AI algorithm to cardiac portion of PET/CT
Radiomics
Cardiotoxicity risk:
• Proceed with cancer therapy
• Consider aggressive trial combinations
Cardiotoxicity risk:
• Send patient to cardiologist for increased surveillance
• Consider cardiac intervention
Cardiotoxicity risk:
• Send patient to cardiologist for increased surveillance
• Consider cardiac intervention
• Consider decreased chemo/immune/radio-therapy dose
• Consider withholding chemo/immune/surgical therapy
• Alter radiotherapy plan

FIG. 10

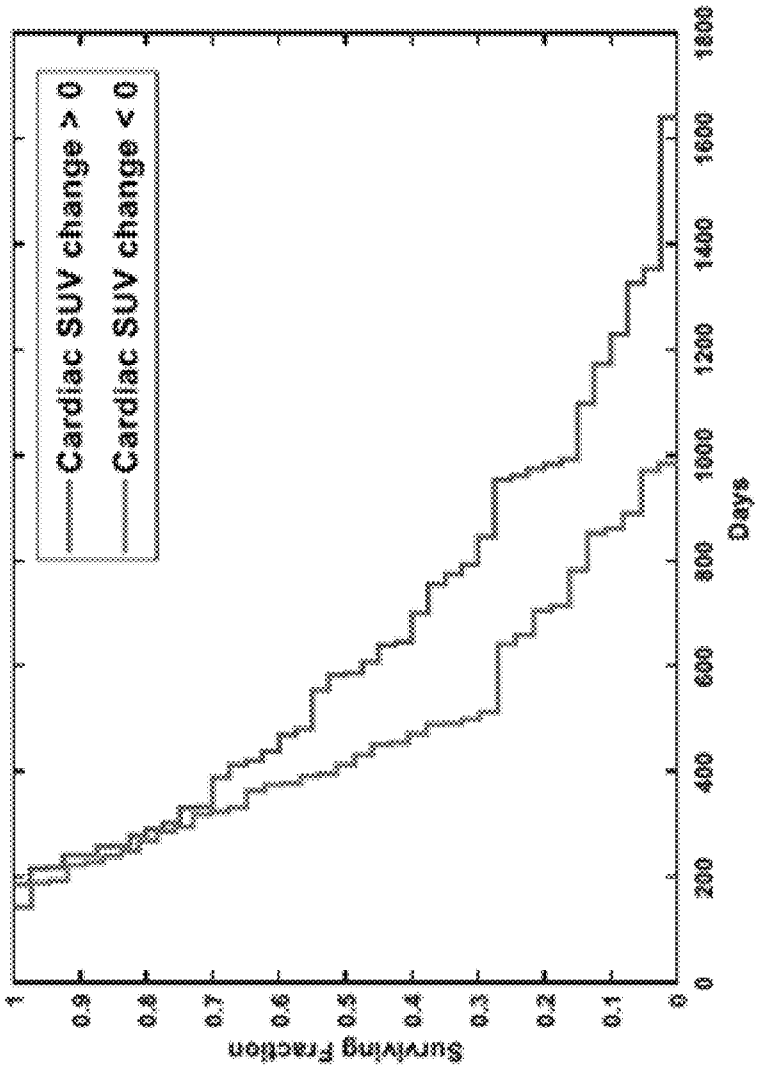
Cardiac SUV change > 0
Cardiac SUV change < 0
Surviving Fraction
Days
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
1000
1200
1400
1600
1800

FIG. 11

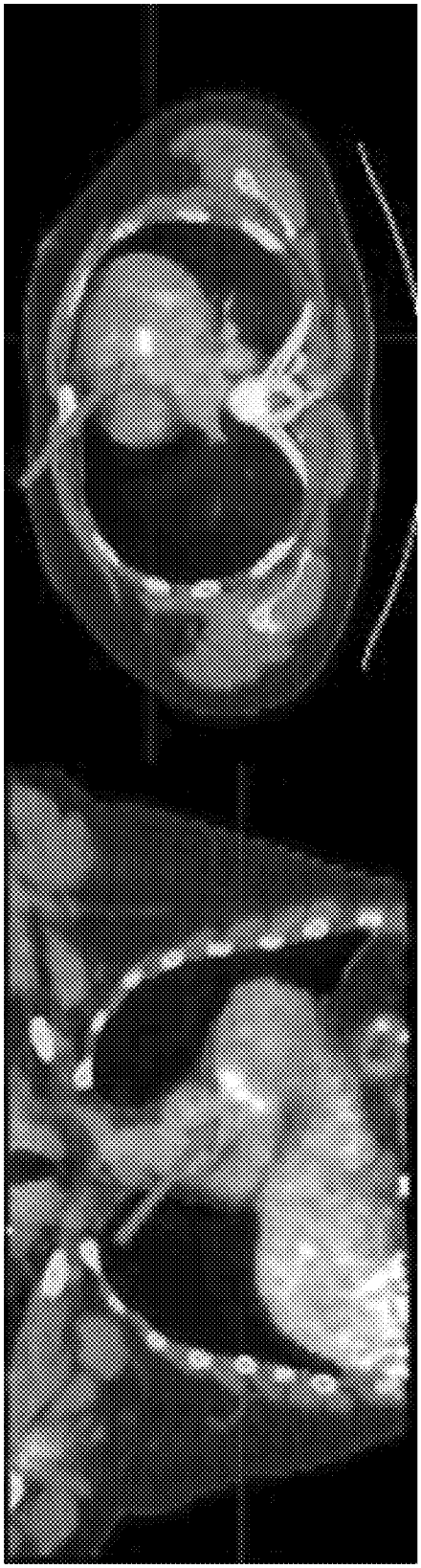

FIG. 12

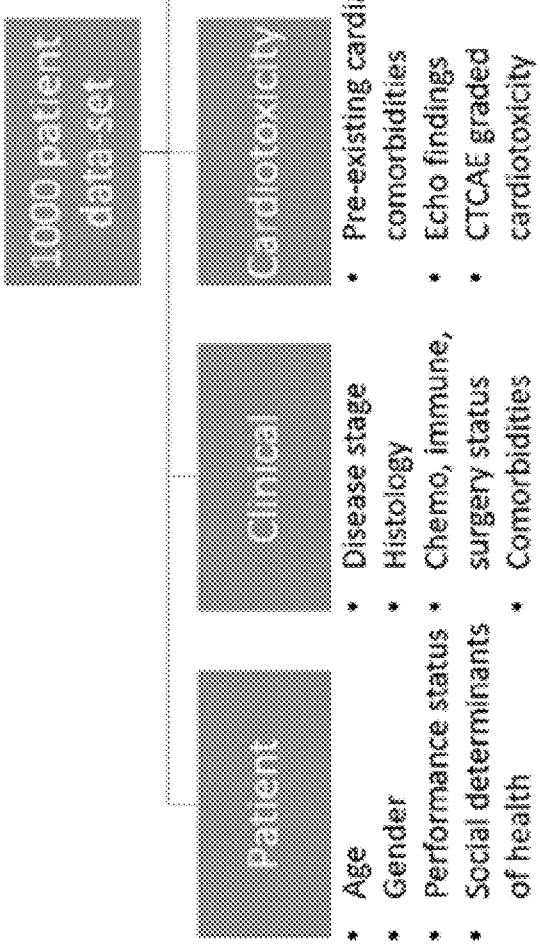
1000 Patient data-set
Patient
Age
Gender
Performance status
Social determinants of health
Clinical
Disease stage
Histology
Chemo, immune, surgery status
Comorbidities
Cardiotoxicity
Pre-existing cardiac comorbidities
Echo findings
CTCAE graded cardiotoxicity
Radiotherapy
Dicom planning CT
Dicom structure set
Dicom dose
Dicom RTPlan
FDG PET-CT
Dicom PET-CT data
Scanner type
Scanner calibration
Blood sugar

FIG. 13

Cardiotoxicity quantification	Examples of cardiotoxicity metrics
Baseline/standard cardiotoxicity metrics	• Patient (age, gender, performance status) • Clinical (pre-existing cardiac conditions, Framingham scores) • Treatment factors (chemotherapy, immunotherapy, molecular therapy, surgery)
Social determinants of health	• Race, ethnicity, Socioeconomic status
Baseline cardiac PET-based metrics	• Cardiac SUV mean, SUV max, SUV peak • Cardiac sub-structure SUV metrics
Cardiac PET radiomics	• intensity-volume histogram metrics, texture features, shape features, and wavelet features, gray-level co-occurrence matrix, gray level dependence matrix • Cardiac sub-structure radiomics
Dose metrics	• Mean heart dose • Volume of heart receiving ≥ 40 Gy • Cardiac dosiomic features
Cardiac Dose-function metrics	• Dose to regions with high cardiac SUV, dose-function histograms, non-linear combinations of dose/function

FIG. 14

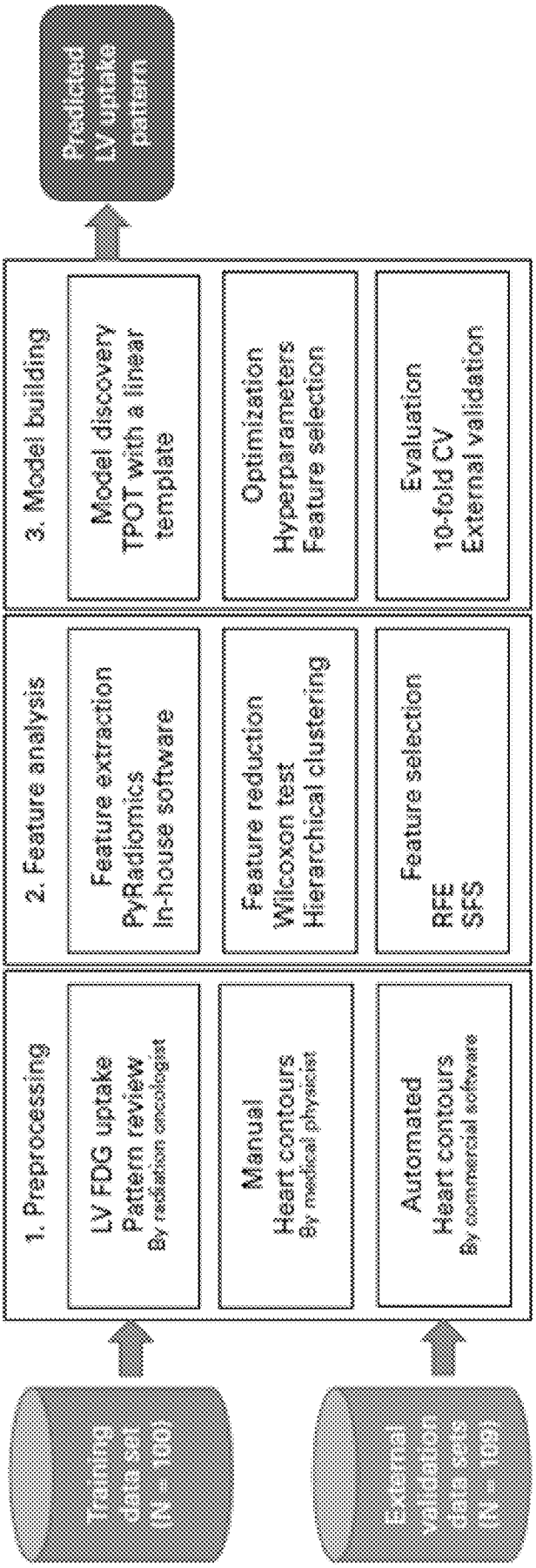
Predicted LV uptake pattern
3. Model building
Model discovery
TPOT with a linear template
Optimization
Hyperparameters
Feature selection
Evaluation
10-fold CV
External validation
2. Feature analysis
Feature extraction
PyRadiomics
In-house software
Feature reduction
Wilcoxon test
Hierarchical clustering
Feature selection
RFE
SFS
1. Preprocessing
LV FDG uptake
Pattern review
By radiation oncologist
Manual
Heart contours
By medical physicist
Automated
Heart contours
By commercial software
Training data set (N = 100)
External validation data set (N = 100)

FIG. 15

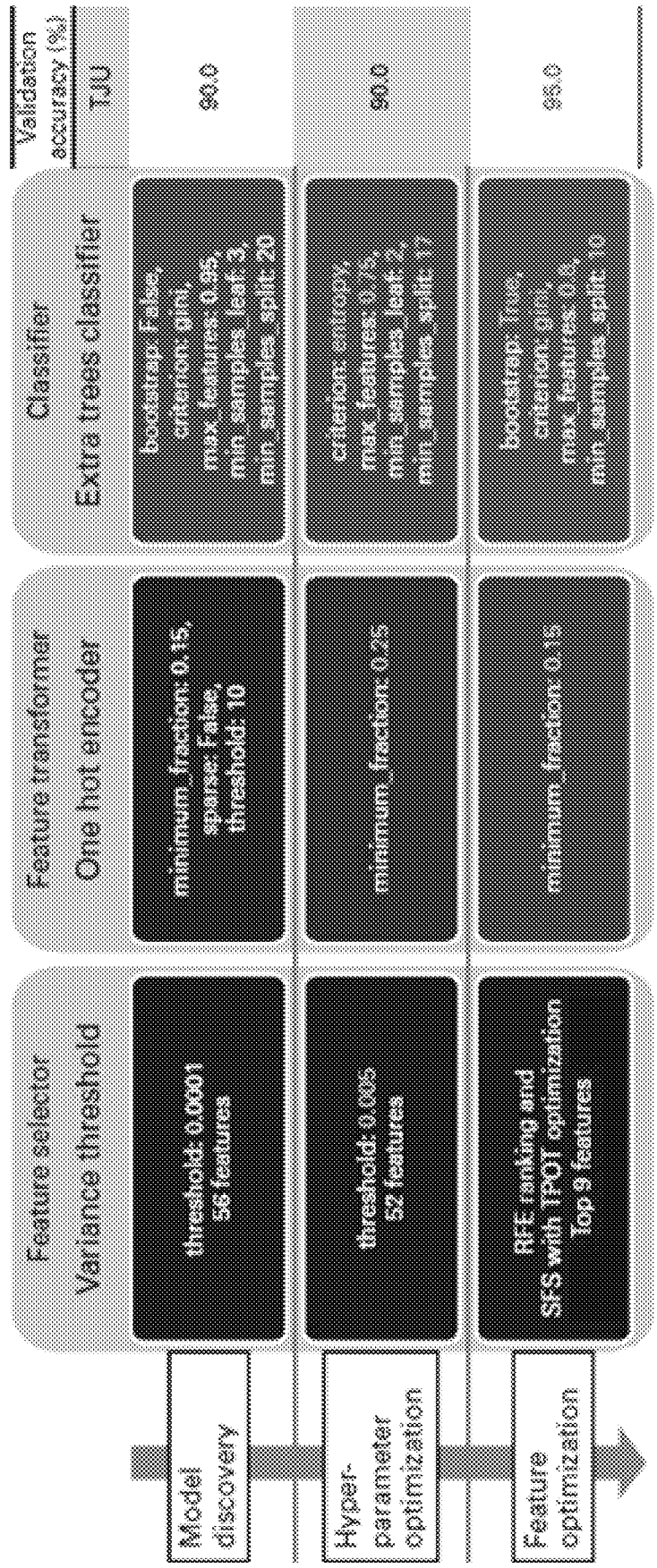
Model discovery
Hyper-parameter optimization
Feature optimization
Feature selector
Variance threshold
threshold: 0.0001
52 features
threshold: 0.005
52 features
RFE ranking and
SFS with TPOT optimization
Top 9 features
Feature transformer
One hot encoder
minimum_fraction: 0.15,
sparse: False,
threshold: 10
minimum_fraction: 0.25
minimum_fraction: 0.15
Classifier
Extra trees classifier
bootstrap: False,
criterion: gini,
max_features: 0.95,
min_samples_leaf: 3,
min_samples_split: 20
criterion: entropy,
max_features: 1.0,
min_samples_leaf: 2,
min_samples_split: 17
bootstrap: True,
criterion: gini,
max_features: 0.1,
min_samples_split: 10
Validation accuracy (%)
TJU
93.0
90.0
93.0

FIG. 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/054863

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***G01N 33/50*** (2023.01); ***G16C 20/70*** (2023.01); ***G06T 7/00*** (2023.01); ***G16B 15/00*** (2023.01); ***G16B 35/00*** (2023.01); *G16B 40/00* (2023.01); *G16C 20/60* (2023.01); *G16H 50/00* (2023.01); *G06N 20/00* (2023.01)

CPC: ***G01N 33/5014; G06T 7/0012; G16B 15/00; G16B 35/00; G16C 20/70;*** *G06N 20/00; G06T 2207/30048; G16B 40/00; G16C 20/60; G16H 50/00*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2023/0349886 A1 (UTI LIMITED PARTNERSHIP) 02 November 2023 (02.11.2023) entire document	1-10
Y	US 2012/0113108 A1 (DALA-KRISHNA) 10 May 2012 (10.05.2012) entire document	5-7
Y	US 2015/0193575 A1 (THE GOVERNORS OF THE UNIVERSITY OF ALBERTA) 09 July 2015 (09.07.2015) entire document	8
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☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHANG et al. "An artificial intelligence approach for predicting cardiotoxicity in breast cancer patients receiving anthracycline." Archives of Toxicology 96.10 (2022): 2731-2737. [Retrieved on 01 January 2025 (01.01.2025) from https://www.researchgate.net/profile/Chung-Feng-Liu/publication/362244666_An_artificial_intelligence_approach_for_predicting_cardiotoxicity_in_breast_cancer_patients_receiving_anthracycline/links/64396b7e1b8d044c63250ba3/An-artificial-intelligence-approach-for-predicting-cardiotoxicity-in-breast-cancer-patients-receiving-anthracycline.pdf] entire document	1-10
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