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Machine Learning-Based Models for Prediction of Toxicity Outcomes in Radiotherapy

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Abstract: The term Machine Learning was invented by Arthur Samuel in 1959, an American pioneer within the field of "Computer Gaming" & "AI" and he said that "it gives computers the power to be told without being explicitly programmed." it's the most growing technical field, lying at the intersection of computing and statistics, and the core of computer science and data science. The adoption of data-intensive machine-learning methods will be found throughout science, technology, and commerce, resulting in more evidence-based decision-making across many walks of life, including health care, manufacturing, education, financial modeling, policing, and marketing. The power of machine learning algorithms to be told from the current context and generalized into unseen tasks would improve the protection and efficacy of radiotherapy practice, resulting in better outcomes.

Effective prediction of toxicity and testing schemes is essential to limit the side effects associated with radiotherapy (RT). In recent years, a growing interest in mechanical engineering (ML) in the scientific community has led to the use of new tools in RT. Several researchers have shown the high efficacy of ML-based models in predicting toxicity. However, the use of these methods in clinics is still delayed, in part due to their low interpretation. Therefore, a review of modern research is needed to familiarize physicians with standard methods and techniques. Here, we present a study of ML-based models for predicting and differentiating RT-induced complications from methodological and clinical perspectives, focusing on the type of hypotheses, ML methods used, and the main results obtained. An overview of our work published research in many areas of cancer, including brain, breast, throat, gynecology, head and neck, liver, lung, and prostate cancer. The purpose is to describe the current state of the art and the key achievements within the field for both researchers and physicians.

Keywords: *Introduction, machine learning, Human-Machine interaction, Radiotherapy, toxicity.*

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Introduction:

It is estimated that about half the world's cancer patients are eligible for radiotherapy (RT), either for therapeutic or therapeutic purposes. Sequential end-generation channels and modern methods, such as intensity-modulated RT (IMRT), stereotactic body RT (SBRT), and proton therapy (PT), provide high accuracy. However, normal tissues close to the target area, defined as endangered organs (OARs), may also be affected, resulting in RT-induced toxicity. Short-term or severe toxicity occurs during treatment or within three months after its completion, and usually, complete recovery occurs between weeks to months. In contrast, recent side effects, such as fibrosis or RT-induced oncogenesis, are generally considered to be irreversible and persistent over time. When planning any RT treatment, its potential benefits should be weighed against the potential for damage to healthy organs and tissues. The ultimate goal is to maximize therapeutic response while minimizing the risk of common tissue problems. On the other hand, when RT is introduced for medicinal purposes, targeted coverage should not be compromised by reaping OAR savings. However, the various side effects of RT vary in their clinical significance. Hence, an accurate estimate of the risks is necessary, especially if alternatives such as surgery or chemotherapy are available. The physiopathology of toxicity is not only related to radiation volume but also depends on genetics and tumor microenvironment. Therefore, identifying key factors that prioritize a particular type of toxin can help improve treatment planning and inform patients and physicians about the expected tolerance of treatment.

On the other hand, data-driven methods assume that interactions between radiation and normal tissue are complex and cannot be adequately represented. Therefore, such methods are intended to identify the most appropriate model for input data (also called attributes or standalone variables) and output data (also called feedback or dependent variables). Toxicity predictions can be classified as "dosimetric," directly related to radiation delivery (ex, dose-volume histogram (DVH)), "clinical," which includes patient and disease-related variables (e.g., sex and tumor histology), as well as “image base” or “radiomic,” which can be extracted from a variety of medical images (e.g., definition, variability, and oblique histograms of image stabilization histograms). These methods can be divided into traditional mathematical methods, such as regression-based techniques, artificial intelligence (AI), and machine learning.

Machine Learning:

Machine learning is a part of AI (artificial intelligence) data as input to predict new output values. That allows software applications to become more accurate at predicting outcomes without being explicitly programmed. Machine learning algorithms use history.

Machine learning is an integral part of the growing field of data science. Algorithms are trained to make categories or predictions through mathematical methods, revealing essential details within data mining projects. This information later drives decision-making within applications and businesses, positively impacting key growth metrics. As big data continues to grow and grow, the market demand for data scientists will increase, requiring them to help identify the most critical business questions and later the data to answer them.

As big data continues to expand and grow, the market demand for data scientists will increase, requiring them to help identify the foremost relevant business questions and, subsequently, the info to answer them.

Machine learning is one of the most exciting technologies that one would have ever come across. As evident from the name, it gives the computer that makes it more similar to humans: The ability to learn. Machine learning is actively used today, perhaps in many more places than expected. We probably use a learning algorithm a dozen times without even knowing it.

ML has proven valuable because it can solve problems at a speed and scale that can't be duplicated by the human mind alone. With massive amounts of computational ability behind one task or multiple specific tasks, machines are often trained to spot patterns in and relationships between input files and automate routine processes.

Machine learning is essential because it gives enterprises a view of trends in customer behavior and operational business patterns, similarly supporting the latest products event. Many of today's leading companies, like Facebook, Google, and Uber, make machine learning central to their operations.

Human Machine Interaction: -

As society becomes more and more knowledgeable, people need a higher level of computer intelligence. Human-computer interaction (HCI) is not limited to real hardware-based interactions. Some of the most intelligent interactions emerge gradually in human lives, such as a series of brilliant techniques related to facial recognition, touch recognition, and voice recognition. Smart programs can help establish communication between people and computers. These simple communication channels have become a major development trend in the HCI sector. The goal of HCI development is naturally to make computers more efficient and adaptable to human needs. It focuses on people rather than forcing people to get used to the computer.

Obtaining data from HCI enables us to learn more efficiently and build more intelligent systems. Machine learning is an essential branch of practical wisdom. It has made great strides in many fields and demonstrated vital research and development (R&D) capabilities. With machine learning technology in HCI, machines are much more intelligent.

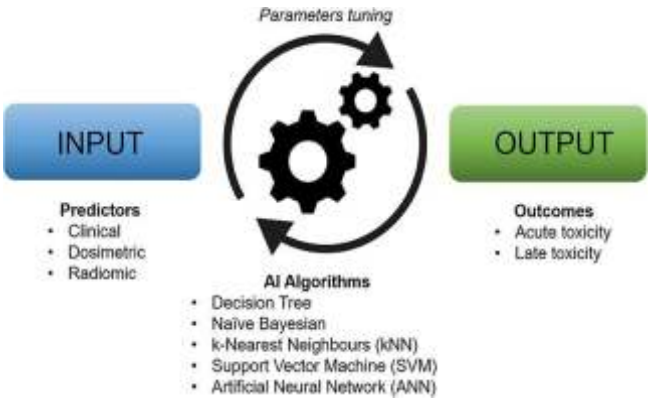
This Special Issue aims to bring together fundamental research and review articles that discuss recent developments in human-machine learning based on machine learning.

Possible Topics Include But Are Not Limited To The Following:

- Voice interaction based on machine learning
- Face recognition and speech based on emotional networks
- In-depth learning models for medical image reshaping, recovery, and registration
- Touch and movement recognition
- Artificial intelligence for intelligent medical analysis
- Smart artificial intelligence detection and diagnostic methods
- Brain-computer interface
- Analysis of human characteristics in machine design

ML-Based Models of Toxicity

The theoretical framework for ML-enabled artificial models was laid down in the 1950s (6). Still, it was not until recently that technological advances allowed the integration of these tools into clinical science testing and treatment. In its broadest sense, AI refers to an active system capable of performing a specific task. ML, often referred to as a subset of AI, usually refers to algorithms that can "perform" particular tasks without explicit use of the solution (although AI and ML terms are often interchangeable). For example, ML algorithms can generate predictions for new and invisible data after training in a limited learning set and are particularly useful for tasks that involve large amounts of data or dynamics (Figure 1). With so many variables that can cause toxicity, ML methods are well suited to match the relationship between adverse drug-induced side effects and related covariates. An ML model that can predict the outcome from an input set after tuning the best collection of parameters in the number of training cases is called a separator. Some of the common categories are naïve Bayes, logistic regression (LR), k-nearest neighbours (kNN), random forests (RF), support vector machine (SVM), and artificial neural networks (ANN).



Overview of Contemporary Research:

Many studies have found that it uses ML-based models to predict RT-related side effects. Most of them affect the head and neck (13 studies), lungs (15 studies), and prostate cancer (16 studies). A small portion focuses on the brain (1 study), breast (studies), 3), esophagus (1 study), gynecology (3 studies), and liver (1 study) cancer (Table 1). The presented books are divided into different categories according to the anatomical region. The focus was on introducing both methodological and clinical aspects.

Cancer type	References	No. of pts	Type of RT	Type of predicted toxicity	Features type	Classifier	Results*
Breast	(10)	90	RT	Dermatitis	R	RF	Acc = 0.87 (test)
	(11)	2277		Moist desquamation, dermatitis, chest pain, fatigue	D, C	LR, RF, gradient boosting	0.56–0.85
	(12)	827	RT	Telangiectasia	D, C	LASSO	
Esophagus	(13)	101	IMRT or 3D-CRT	Pneumonitis	D, C	LR	Acc = 0.63
Gyneco	(14)	42	EBRT+BRT	Rectal toxicity	D	SVM	0.82–0.91
	(15)	42	EBRT+BRT	Rectal toxicity	D	CNN (transfer learning)	1.29
	(16)	35	BRT	Fistula formation	D, C	SVM	1.30
H&N	(17)	437	RT (397) PT (40)	Toxicity (grade ≥3)	C	LR, RF, XGBoost	0.63–0.65
	(18)	2121	RT	Unplanned hospitalizations, Feeding tube placement, Weight loss	D, C	LR, gradient boosting, RF	0.64–0.76
	(19)	153	RT	Xerostomia	D, R, C	6 ML algotithms	Best SVM and extra-trees 0.74–0.89
	(20)	86	RT	Trismus	D	IBDM	Identification of a cluster of voxel related with toxicity
	(21)	427	RT	Xerostomia	D, C	LR, LASSO, RF	Best LR (0.70)
	(22)	173	RT	Acute dysphagia	D, C	SVM, RF	0.82
	(23)	297	IMRT	Xerostomia (grade ≥2)	D, C	LR	Model updating is beneficial
	(24)	134	IMRT and PT	Esophagitis	R, D	LASSO	0.75
	(25)	47	3D-CRT	Sensorineural hearing loss	R, C	Decision stump, Hoeffding	76.08% accurarcy 75.9% precision
	(26)	37	IMRT	Parotid shrinkge Xerostomia	D, C	Fuzzy logic Naïve Bayes	Acc = 0.79–0.86
	(27)	249	IMRT	Xerostomia, sticky saliva	R, D	Multivariate LR	0.77
	(28)	351	IMRT	Mucositis	D, C	LR, SVM, RF	0.71 (RF)
	(29)	1 (H&N) 1 (Prostate)	IMRT	Xerostomia (H&N), Rectal bleeding (prostate)	D	Decision tree, SVM	0.42% MAE (H&N) 97% acc (prostate)
Liver	(30)	125	SBRT	Hepatobiliary toxicity	D, C	CNN (transfer learning)	1.25
Lung	(31)	110	SBRT	LC, DFS, OS, and fibrosis	R	Cox regression	
	(32)	203	IMRT or PT	Pneumonitis	C	RF	1.06
	(33)	192	IMRT and 3D-CRT	Radiation pneumonitis	R, D, C	LASSO	0.68
	(34)	197	SBRT	Chest wall syndrome	D, C	Descision tree RF	n/a
	(4)	3496 (lung+brain +H&N)	RT	Classifiers comparison	D, C	Decision tree, RF, ANN, SVM, elastic net, logit-boost	Best: elastic net LR and RF
	(35)	14	SBRT	Lung injuries	R, D	LR	0.64–0.78
	(36)	201	SBRT	Pneumonitis	D, C	Decision trees, RF, RUSBoost	
	(37)	115	RT	Esophagitis	D, C	LASSO	0.78
	(38)	54	3D-CRT	Pneumonitis	D, C	Bayesian network LR Single variable	0.66–0.83

	(39)	748	RT	Esophagitis	D, C	LR	0.83
	(40)	219	3D-CRT	Pneumonitis	D, C	SVM	1.16
	(41)	55 (H&N) 219+166 (Lung)	3D-CRT	Xerostomia, Pneumonitis (166) Esophagitis (216)	D, C	LR, SVM, ANN	Best: modified SVM
	(42)	219	RT	Radiation pneumonitis	D, C	Decision tree, ANN, SVM, self-organizing maps	0.79
	(43)	234	RT	Radiation pneumonitis	D, C	Decision tree	0.72
	(44)	166	EBRT	Esophagitis xerostomia	D	LR	
	(45)	142	3D-CRT	Pneumonitis	D	ANN	0.61–0.85
Prostate	(46)	64	IMRT (52 pts), 3D-CRT (12 pts)	Urinary toxicity Gastro-intestinal toxicity	R, D, C	LR	0.65–0.77
	(47)	33	IMRT	Cystitis	R	LR	0.62–0.75
	(48)	33	IMRT	Rectal wall changes	R	LR	0.46–0.81
	(49)	351	RT	Rectal bleeding Fecal incontinence Urinary incontinence Nocturia	R, D, C	LR	0.58–0.73
	(50)	598	RT	Late fecal incontinence	D, C	ANN	0.78
	(51)	593	RT	Rectal bleeding	D, C	ICA	0.83, 0.80, 0.78
	(52)	324	BRT+-EBRT	GU toxicity symptoms	D, C, G	RF	0.7
	(53)	118	EBRT, BRT	GI toxicities	D	LR	Identification of spatial constraint for toxicity reduction
	(54)	368	RT	Rectal bleeding, Erectile dysfunction	C, G	RF, LR	0.71 (rectal bleeding) 0.68 (erectile dysfunction)
	(55)	79	IMRT	Rectal toxicity (grade ≥2)	D, C	LR	1.28
	(56)	754	EBRT	Dysuria, hematuria, incontinence, frequency	D, C	LR, Elastic-net, SVM, RF, ANN, MARS	Best: LR, MARS AUC = 0.65
	(57)	99	EBRT	Rectal bleeding	D	LDA, SVM, k-means, kNN, PCA, CP-DMA	Best: CP-DMA
	(58)	261	3D-CRT	Rectal toxicity, rectal bleeding	D, C	RF NTCP, NTCP	0.76, 0.66
	(59)	718	RT	Rectal bleeding		LR, ANN	0.655, 0.704
	(60)	321	RT	Acute bladder and rectal toxicity	D, C	ANN, SVM	0.7
	(61)	119	RT	Rectal bleeding Nocturia	D	ANN	Sensitivity and specificity >55%

*3D-CRT, 3D conformal RT; Acc, accuracy; ANN, artificial neural network; AUC, area under the curve; BRT, brachytherapy; CNN, convolutional neural network; CP-DMA, canonical polyadic decomposition–deterministic multi-way analysis; DFS, disease free-survival; EBRT, external beam RT; GI, gastrointestinal; GU, genitourinary; H&N, head and neck; IBDM, image-based data mining; ICA, independent component analysis; IMRT, intensity-modulated RT; kNN, k-nearest neighbors; LASSO, Least Absolute Selection and Shrinkage Operator; LC, local control; LDA, linear discriminant analysis; LR, logistic regression; MAE, mean absolute error; MARS, multivariate adaptive regression splines; ML, machine learning; NTCP, normal tissue complication probability; n/a, not applicable; OS, overall survival; PCA, principal component analysis; pt, patient; PT, proton therapy; RF, random forest; RT, radiotherapy; RUSBoost, random under-sampling Boost; SBRT, stereotactic body RT; SVM, support vector machine. Features were classified as clinical (C), dosimetric (D), genomic (G), or radiomic (R). *If not specified, AUC values are reported.*

Brain:

One study of ML-based toxicity modeling was related to brain cancer [4]. In the study, the authors compared the performance of different ML dividers on multiple data sets, including patients with brain, lung, and H&N primaries. Their models included trunks, RF, neural network, SVM, elastic net LR, and Logit-Boost categories and were tested on 12 different data sets for 3496 patients. Both dosimetric and blood markers from meningioma and (non-lung cancer) - small cells (NSCLC) and patients with H&N cancer were considered. No single category is valid for all data sets, but RF and net LR work equally well (best for six and four data sets, respectively). Based on these findings, the authors re-examined the pre-segment selection criteria, concluding that strong segment selection is beneficial, resulting in an AUC average of 0.02.

Gynecological Cancers:

Three studies in this section analyze the prediction of toxic effects following brachytherapy alone or combined with external RT (EBRT) in gynecological cancer. All models are trained with limited data sets, ranging from 35 and 42 patients, and SVM or convolutional neural network (CNN) class dividers.

Tian et al. [5] developed a fistula modeling model with an SVM filter. Thirty-one factors were used as predictive variables from a small sample of 35 patients treated with interstitial brachytherapy. Their model has reached a maximum accuracy of 0.901, but the authors aptly point out the strong limit of using a small data set.

Head and Neck:

The size of the training data sets for published works related to H&N cancer from 37 to 2121 patients. Predicted toxic effects included late xerostomia, acute mucositis, parotid shrinkage, unexpected hospitalization, and weight loss. The classifications used include LR, RF, gradient boosting, and one based on an abstract concept. In addition, one [4] study compared the performance of different class dividers in other data sets (please refer to the Brain section for more details).

The two most recent articles [1], [3] both used three different categories (RF, gradient boosting, and LR models) to predict random sleep, feed tube placement, and significant weight loss (Reddy) and grade thi3 toxicity. Reddy et al. considered an extensive data set of 2,121 patients, comparing more than 700 treatment-related clinical variables, and achieved AUC values of 0.640, 0.755, and 0.751 in RF, gradient boosting, and LR, respectively. They succeeded in predicting grade ≥3 toxicity in 437 patients after 90 and 180 days (c-0.65 and 0.63 counts, respectively) using 47 patient covariates. The critical volume planning target (PTV), body mass index (BMI), essential volume in regions outside of PTV, and age had significant statistical implications.

Lungs:

The data set size was between 54 and 235 patients for lung cancer. Most studies focused on radiation-induced respiratory disease, and other studies focused on esophagitis, xerostomia, sticky saliva, and chest pain. RT lung cancer may cause chest pain due to fractures of the ribs, neuropathy-induced neuropathy of the intercostal nerves or nerve branches, chest wall edema, or chest wall fibrosis. However, the only study we found was that the chest pain was directly investigated [4]. The authors used a decision-making tree and RF methods to identify the strong predictors of chest wall pain in a group of 197 patients. Both static and multiple analyses confirmed the role of rib capacity at one cc, chest wall volume up to 30 cc, and rib dose max (Dmax) as the appropriate variable. Based on these findings, efforts should be made to reduce rib capacity to 1 cc <4000 cGy, chest wall capacity to 30 cc <900 cGy, and rib Dmax <5100 cGy to reduce chest wall disease.

Radiotherapy:

With the continued growth of patient-centered radiotherapy data from multimodality molecular and biotechnology sources, Response-adapted radiotherapy (KBR-ART) emerges as an important area for personal radiation oncology treatment. In KBR-ART, the planned dose distribution can be adjusted based on the criteria used in patients' clinics and geometric and biological parameters. In this paper, we present current developments in adaptive radiotherapy (ART), advances in KBR-ART, and explore a few static and flexible machine learning methods applications to detect the strength of the KBR-ART framework enhancing tumor control and reduction. Adverse effects in respect of patients treated with individual radiotherapy. Specifically, three questions required for the implementation of KBR-ART are considered: (1) what information is required; (2) how to accurately measure RT results; and (3) how to adapt best. The different machine learning algorithms for the KBR-ART application will be discussed and compared. Examples representing different stages of KBR-ART are also visited.

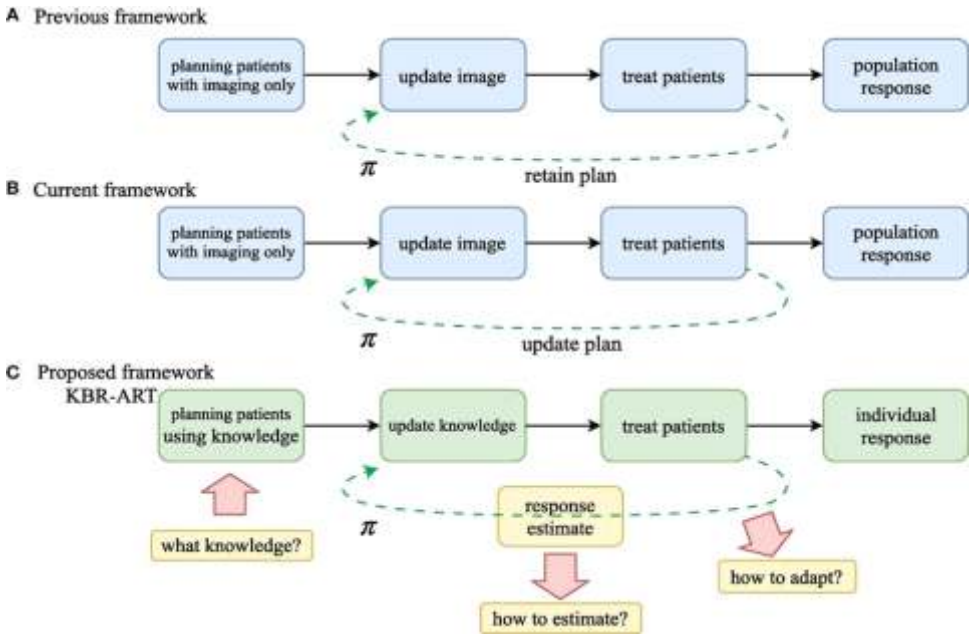


Fig. 1. Comparison of the workflow of (A) non-adaptive RT, (B) current image-based ART, and (C) the proposed KBR-ART approach. The current ART (B) mainly relies on image guidance such as computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). In KBR-ART, the planning patients' stage can utilize general knowledge about patient status (imaging + biological markers) as information for adapting treatment instead of using imaging only. Two significant differences between previous/current RT and KBR-ART are that (1) knowledge is no longer restricted to imaging only and can include biological markers such as tumor genetics or blood-based inflammatory proteins (cytokines) to inform predictive modeling and decision-making, and (2) application process of machine learning for adapting a treatment plan π in KBR-ART.

A significant natural advantage of the KBR-ART framework is that treatment planning will be designed to adapt flexibly to ongoing changes during treatment to improve radiotherapy goals to eradicate the tumor while minimizing injury to the normal excluded tissue based on individual patient characteristics. As shown in Figure 1, the treatment plan can be legally implemented according to the decision-making process π. This is illustrated in Figure 1A of the previous/current framework, where π is static. Still, in the case of KBR-ART, Figure 1B, π is a time-dependent function based on the information (information updates) available. During treatment. The following scenario can be used as an example of how KBR-ART can be used in practice: a given planned radiation course is considered appropriate according to the first human-based model as a dose-based controlling (TCP) and standardized control. The potential for tissue problem (NTCP) and the goal is to develop a mild tumor control [p + = TCP · (1 – NTCP)], for example. Then, during partial radiotherapy treatment, the patient did not achieve the predicted amount of TCP as expected, or worse, suffered from unexpected toxicity due to treatment, i.e., NTCP exceeded the intended risk limit. This is where KBR-ART comes into play; to learn from the current observation.

Q: What Knowledge to be Used for KBR-ART Planning?

There are four significant types of RT data that are potentially useful as part of the knowledge synthesis for

KBR-ART:

- *Clinical data,*
- *dosimetric data,*
- *radionics data,*
- *and biological data.*
- *Clinical Data*

Clinical data refers to cancer diagnostic factors (e.g., distance, stage, history, site, etc.), survival metrics (e.g., blood cell counts, heart rate/heart rate, lung measurements, etc.), and patient-related information (e.g., related diseases, gender, age, etc.). Because of their nature, clinical data can often be obtained in an informal format that can be challenging to extract information directly. Therefore, machine learning methods for processing natural language can help convert such data into a structured layout (e.g., included in a table) before further processing.

Dosimetric Data

Dosimetric data contains information on the treatment plan for RT, which includes radiation dose calculations using computed tomography (CT) imaging. In particular, dose-volume metrics obtained without histograms (DVHs) were extensively investigated to model the outcome (12-16). Valuable metrics are usually a volume that receives a large volume or equal to a specific volume (Vx), a small volume to a very high degree of x% of the volume (Dx), average, limit, minimum volume, etc. Significantly, dedicated MATLAB ™-based software called "DREES" can automatically detect metrics and apply them to RT response prediction models.

Radiomics Data

Radiomics is a field of medical thinking research that aims to extract the essential aspects of value from medical imaging and to link this knowledge to clinical and biological conclusions. The most common form of imaging is CT, considered a standard treatment plan for RT. Other imaging techniques used to improve treatment monitoring and prognosis for various types of cancer are also used, such as positron emission tomography (PET) and magnetic imaging resonance (MRI). These methods can be used individually or in combination.

Biological Data

According biomarker is defined as "a factor that is properly measured and evaluated as an indicator of common biological processes, pathological processes, or pharmacological responses to medical interventions." Biomarker measurements are usually based on tissue or liquid specimens, which are analyzed using biological laboratory techniques and have the following two categories according to their physical and chemical sources:

Conclusion:

This study presented a comprehensive design framework for KBR-ART and application based on machine learning and examined some of its key features. First, in Section 2, we analyzed the characteristics and types of elements in clinical data, such as the effective selection of data entry for KBR-ART. Second, in Phase 3, we visited a few promising and powerful modern development techniques, such as DNNs, CNNs, RNNs, and older line-type retrospective models. The framework of the KBR-ART we have developed here is based on machine learning strategies, accurate predictions, and sequential learning, which are the basis for building the KBR-ART system. There are three questions about the design and implementation of KBR-ART, which we have discussed in this paper and presented illustrative examples of each highlighted RL / BN application in the NSCLC radiation therapy database. Section 4 provided the integration structure in Section 4.1 of the KBR-ART system design (Figure 18). The aim was two fold: (1) to clearly understand the context of past ART built into the last generation and (2) to provide a guiding principle for designing the next-generation algorithms.

Despite loose conclusions about the clinical use of RT-induced toxicity models, our findings suggest that ML-based solutions for RT toxicity prediction may represent a valuable tool in research settings. An effective toxicity predictive system is essential to increase the RT treatment index and guide the clinical selection of patients. Such models can be a vital asset in many different areas for patients and nurses.

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