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RADIOGENOMICS IN ONCOLOGY: A COMPREHENSIVE STUDY OF VARIOUS ONCOLOGICAL DISORDERS

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Abstract. The emergence of artificial intelligence in the digital era has brought about a significant transformation in the field of clinical decision support systems. The advent of technological advancements has led to the development of novel data-driven analytical algorithms, hence greatly augmenting human capacity to process information. The field of cancer radiogenomics presents a promising area within the realm of precision medicine. The objective of our research is to enhance our understanding of the genetic factors that contribute to the formation of tumors. This will be achieved by integrating extensive radiomics features extracted from medical imaging, genetic data obtained from clinical-epidemiological sources, and insights derived from high-throughput sequencing using mathematical modelling techniques. The aim of integrating radiomics and genomes is to gain a deeper understanding of the complex mechanisms behind cancer growth. The primary aim is to develop novel, empirically supported methodologies for the identification, prediction, and individualized therapeutic strategies for cancer, utilizing the acquired understanding. This comprehensive review aims to provide an overview of the existing body of research on the applications of radiogenomics, with a specific focus on solid malignancies. Additionally, we will examine the barriers that are now preventing the widespread integration of radiomics into therapeutic contexts.

Key words: Quantitative Imaging, Radiogenomics, Radiomics, Genomics, radiomics features, Machine Learning.

1. Introduction. Tissue biopsy remains the metric for cancer diagnosis but presents significant limitations its invasiveness, cost, and impracticality for serial monitoring make it less than ideal. In modern oncology, medical imaging serves as a fundamental aid for biopsy guidance, enhancing tumor localization and tissue sampling accuracy [1]. Imaging markers can be qualitative, quantitative, or numerically measurable attributes. The latter are the focus of radiomics, a computational approach that extracts numerous features from imaging modalities such as MRI, CT, and PET. Radiomics transform these features into actionable data, revealing patterns and correlations not immediately apparent through visual inspection. The technique offers significant promise for non-invasive disease diagnosis, prognosis, and treatment planning, thereby paving the way for personalized healthcare [2].

Genomics has revolutionized our understanding of the genetic basis of diseases, offering insights valuable for precision medicine, screening, and diagnosis. However, a significant knowledge gap persists between tissue-level imaging data and genomic information, often resulting in either over-treatment or under-treatment due to the lack of comprehensive biological markers [3].

The field of radiogenomics has recently emerged as an interdisciplinary intersection, combining the methodologies of radiomics, which involves the extraction of quantitative information from medical images, with genomics. This confluence allows for the elucidation of correlations between imaging phenotypes and genomic traits, providing a holistic approach to disease understanding and treatment planning. Notably, initial applications of 'Radiogenomics' were aimed at predicting genomic alterations from radiation therapy but have since evolved to encompass a broader range of diagnostic and prognostic capabilities [4, 7]. By leveraging data-rich patient cohorts, radiogenomics research has commenced linking imaging attributes such as tumor morphology to molecular phenotypes, a step pivotal for enhancing precision medicine, especially in oncological contexts."

This manuscript is structured in the following manner: Section 1 delves into the basic principles of radiomics and genomics. Section 2 details the radiogenomics workflow. Section 3 presents a comprehensive analysis and review of existing radiogenomics investigations. Section 4 presents a synthesis of radiogenomics applications

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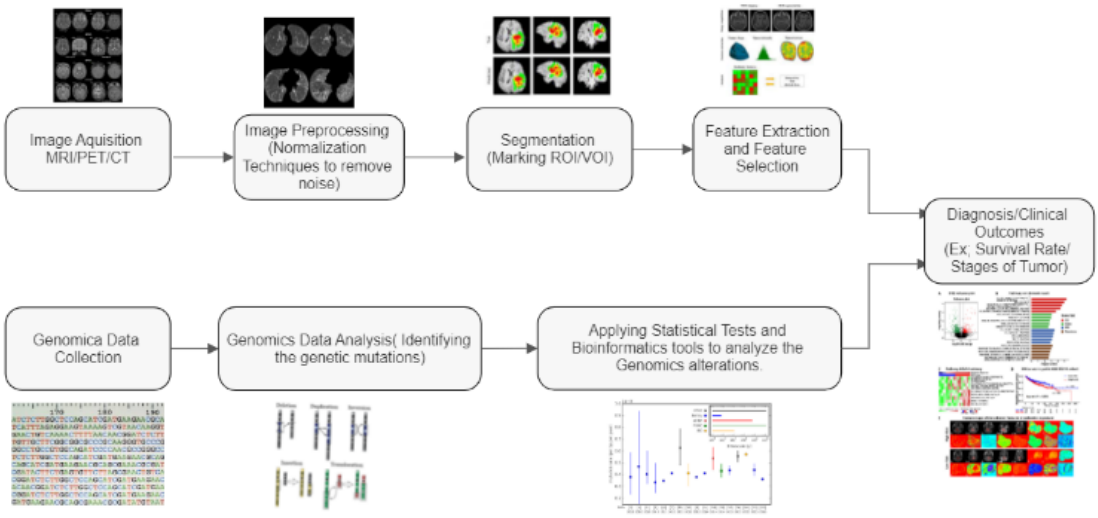

Fig. 2.1: Radiogenomics pipeline

across diverse cancer types. Section 5 highlights the constraints of such methodologies. Section 6 elaborates on the applications of radiogenomics. Finally, Section 7 concludes the paper and points towards potential avenues for future research.

2. Overview of Radiogenomics Pipeline. The term "Radiogenomics" refers to the relatively new field that deals with the rapid processing of radiological images and genetic information into high-dimensional information to conduct research.

Figure 2.1 represents the workflow of Radiogenomics, The radiomics and genomics pipeline involves several stages, and the implementation of radiogenomics is the integration of the data and knowledge obtained from both radiomics and genomics analyses.

Radiomics pipeline: It comprises the following steps: Acquisition of image, Image Pre-processing, Segmentation (ROI), Feature Extraction, Feature Selection, lastly Model Development and Validation with Disease Classification

2.1. Radiomics pipeline. It comprises the following steps: 1. Acquisition of image, 2. Image Pre-processing, 3. Segmentation (ROI), 4. Feature Extraction, 5. Feature Selection, lastly 6. Using machine learning creating prognostic and predictive models.

Image Acquisition. For the purpose of performing radiomics analysis, the original medical images are required. PET/CT/MRI have been used to aid in the detection and treatment of cancer. Images give precise details regarding the functional and structural tumor characteristics. Due to the significant advancements in medical imaging technology, radiomics has become a promising tool for addressing the challenging oncology challenges. Multi-slice CT has replaced single-slice CT in the development of medical imaging systems, enabling dynamic radiomics at various time points. CT has also been investigated to enhance the detection of tissue density [8]. Diffusion-weighted MRI can track the density, volume of tumors, and the effectiveness of cytotoxic therapy (chemotherapy that uses cytotoxic drugs).

Image Pre-processing. The pre-processing step is essential to gain a better high-quality image for the next analysis. photo processing steps normally consist of photograph normalization, noise removal, bias correction, interpolation and reprocessing, motion correction, and thresholding [9].

Scientific image analysis is based on the concept of picture normalization, which involves altering the range of pixel values. All records are generally implemented using standard techniques including size normalization,

histogram normalizing, and spatial normalization. Current paintings demonstrate not unusual normalization functions on more than one dataset that offer accuracy to the unique photos and enhance image segmentation.

The main function of picture noise discount is to keep the maximum vital capabilities of the photograph even as removing unimportant capabilities. Classical noise removal techniques include spatial domain filtering and variable noise removal techniques. present transform area methods together with the Fourier rework, cosine remodel, wavelet discipline technique, and sparse 3-D filtering are all advanced from the authentic spatial field approach. picture resampling is split into up-sampling and down-sampling. according to the Photo Biomarker Standardization Initiative (IBSI) [10], facts from one-of-a-kind fashions may be suitable for exceptional picture formats. movement correction is a manner to take away movement blur in a photo, which is also an important prerequisite to attaining a photo replica with the right improvement.

Segmentation of Image. The technique of segmentation involves dividing a picture into areas according to visual characteristics such as color, texture, density, or motion. The segment created must match the object, border, or detail area of the image [10].

Three main methods are used to segment 2-D ROI (Regions of Interest) or 3-D VOI (Volumes of Interest):

Manual Segmentation. Professional authors manually plot ROI / VOI or slice each image by ROI / VOI or manual segmentation or definition. processing section. Using this method, the segmentation process can be precisely controlled, as the description can take into account even the smallest changes and changes. However, it is time-consuming and leads to differences among observers.

Semi-automatic segmentation. Semiautomatic segmentation combines manual and automatic methods. Initially, an automated method or technique is used to provide the initial segmentation of the ROI/VOI. Users can manually update and adjust the results if needed. This approach reduces manual effort and speeds up the process while allowing users to make necessary adjustments. Examples of semi-automated processes include automated-based methods followed by manual optimization.

Fully automatic segmentation. Automatic segmentation refers to a fully automatic method of segmenting ROI / VOI without manual intervention using computer algorithms and machine learning. These algorithms analyze image quality such as density, texture, or shape to identify and isolate areas of interest. Automatic segmentation is generally faster and less prone to human error, but there may be differences depending on the actual algorithm used. Examples of automated segmentation techniques include clustering, edge algorithms, machine learning techniques (MI) like, CNN(convolutional neural networks), and watershed segmentation. When these methods were compared, semi-automatic segmentation was found to be the best.

ROI/VOIs delineate regions of interest in radiographs for analysis. Manual segmentation, a common approach in previous studies, doesn't involve post-processing software but is time-consuming and impractical for large datasets. Human-based delineation introduces observer-induced bias, affecting robustness due to inter-observer and intra-observer variance. Semi-automatic methods employ algorithms for ROI/VOI segmentation but may need manual correction and calibration.

Some major open-source or commercial software examples are, ITK-SNAP, 3D Slicer, ImageJ, and MITK LIFE are available as a partial partition. Automatic segmentation is based entirely on deep learning using artificial neural networks [11]. Deep learning techniques have numerous applications in automatic image recognition, particularly through Convolutional Neural Networks (CNNs). CNNs excel in computer vision tasks like image recognition and classification by extracting features directly from input data. The advantage over radiomics lies in automatic feature extraction and precise classification. However, deep learning typically requires a substantial number of medical image samples, especially when distinguishing cancerous areas from normal tissue with significant signal differences [13].

Feature Extraction. Segmented areas are used to extract features. Image features in medical imaging studies give crucial insights about various anatomical structures, physiological activities, and clinical conditions. Qualitative or quantitative. Radiologists and doctors may use qualitative aspects to evaluate images. Shape, margin, density, intensity, homogeneity, distribution, pattern, enhancement, calcifications, and anatomic position are described. These traits help diagnose and characterize many diseases and provide visual indications. Quantitative characteristics are calculated from imaging data and involve numerical values. Advanced image processing or automatic algorithms gain these traits.

Segmented ROIs/VOIs yield shape, statistical, and texture radiomics features. Flatness, elongation, surface

Table 2.1: Categories of quantitative radiomics features.

Category	Description	Formula
First Order Features	Basic statistical measures of pixel intensities	
	Mean	$\text{Mean } = 1/N \sum_{i=1}^{N} x_i$
	Median	Value at the middle position of the sorted intensity values.
	Standard deviation	$\sqrt{\frac{1}{N-1} \sum_{1=1}^{N} \left(X_1 - \bar{X}\right)^2}$
	Skewness	$\frac{\frac{1}{N} \sum_{1=1}^{N} (x_1 - \bar{X})^3}{\left(\frac{1}{N} \sum_{1=1}^{N} (x_1 - \bar{X})^2\right)^{\frac{3}{2}}}$
	Kurtosis	$\frac{\frac{1}{N} \sum_{1=1}^{N} (X_1 - \bar{X})^4}{\left(\frac{1}{N} \sum_{1=1}^{N} (x_1 - \bar{X})^2\right)^2}$
Shape-based Features	Geometric properties of the tumor shape	
	Volume	Number of voxels within the tumor region of interest.
	Surface Area	Total surface area of the tumor region of interest.
	Compactness	$\frac{\text{Surface Area}}{\text{Volume}^{\,3}}$
	Sphericity	$\frac{\pi^{\frac{1}{3}} \times \left(6 \times \text{Volum}^{\frac{2}{3}}\right)}{\text{Surface Area}}$
Texture-based Features	Quantify spatial patterns within the tumor	
	GLCM (Gray-level Co-occurrence Matrix) features	Various features can be derived, such as contrast , energy, homogeneity, etc., based on the co-occurrence matrix of image intensities.
	GLRLM (Gray-level Run Length Matrix) features	Various features can be derived, such as short-run emphasis, long-run emphasis, gray-level non-uniformity, etc.
	GLSZM (Gray-level Size Zone Matrix) features	Various features can be derived, such as zone size entropy, zone percentage, zone variance, etc.
	Gray-level Dependence Matrix (GLDM) features	Various features can be derived, such as contrast, dissimilarity, homogeneity, etc., based on the dependence matrix of image intensities.
	NGTDM (Neighborhood Graytone Difference Matrix) features	Various features can be derived, such as coarseness, contrast, busyness, etc., based on the neighborhood gray-tone difference matrix.
Higher-order Features	Derived from the gray-level co-occurrence matrix (GLCM)	
	Contrast	$\sum_{\mathrm{I},j} P(i,j) \cdot (i,j)^2$

area, sphericity, voxel volume, and surface volume are shape characteristics. They express the lesion form, voxel intensity histogram, and texture. They can be taken directly from photos or after filters or transforms like wavelet transform. Table 2.1 lists the many quantitative radiomics features.

Feature selection. After features have been extracted, they are evaluated using a variety of statistical techniques to determine which ones are highly correlated from the desired results. Feature selection is a process used in radiomics to identify and select a subset of relevant features from a larger set of features extracted by the medical images. The aim is to improve the accuracy and efficiency of predictive models and reduce the dimensionality of the feature space. Table 2.2 describes the different methods for feature selection.

Model Development and Validation with Disease Classification. - In this pivotal stage, machine learning and statistical models are developed using integrated data, comprising radiomic, genomic, and clinical information.

- The models go through a rigorous evaluation process, which includes testing their performance using methods like cross-validation, ROC analysis, and calibration assessments. This ensures that the models work effectively and provide accurate results.

- These models are designed not only to predict patient outcomes, treatment responses, and other clinically relevant endpoints but also to excel in the accurate classification of diseases.

The utmost emphasis is placed on ensuring the reliability and generalization capabilities of these models, positioning them for invaluable clinical applications that includes disease classification, prognosis, and treatment optimization.

Table 2.2: Methods for feature selection

Type of Feature Selection Algorithm	Examples
Filter Methods	- Correlation based feature selection - Mutual information based feature selection - Chi-square feature selection
Wrapper Methods	- Recursive Feature Elimination (RFE) - Forward/Backward Feature Selection
Embedded Methods	- LASSO (Least Absolute Shrinkage and Selection Operator) - Elastic Net - Random Forest based feature selection - Gradient Boosting based feature selection
Regularization Methods	- L1 Regularization (Lasso) - L2 Regularization (Ridge)
Dimensionality Reduction Techniques	- PCA (Principal Component Analysis) - LDA (Linear Discriminant Analysis)

Table 2.3: Process of data acquisition and data preprocessing

Data Acquisition	Obtaining biological samples and their genetic data. − DNA Sequencing: Determining the order of nucleotides in a DNA sample. − Microarray Analysis: Analyzing gene expression levels for thousands of genes simultaneously. − Genotyping: Assessing specific genetic variations like SNPs.
Data Pre-processing	− Ensuring data quality, consistency, and readiness for downstream analysis. −Quality Control: Identifying and removing low − quality or erroneous data. −Data Transformation: Converting data into a suitable format for analysis if needed.

2.2. Genomics Pipeline. It includes the following steps genomics data acquisition and preprocessing, Genomic data analysis, Statistical analysis and modelling.

(i) Data Acquisition and Preprocessing: Collecting genomic data, such as gene sequencing or genetic profiling, from the same patients whose imaging data were used in the radiomics pipeline. Preprocessing ensures data quality and consistency shown in Table 2.3.

(ii) Genomic Data Analysis: Genomic Data Analysis is a crucial step in the genomics pipeline. It involves processing and interpreting genetic information from biological samples. Key components include variant calling, gene expression analysis, functional annotation, pathway analysis, statistical methods, and data visualization. The results contribute to scientific understanding and personalized treatment decisions.

(iii) Statistical Analysis and Modeling: Applying statistical tests and bioinformatics tools to examine the relationship among genomic alterations and clinical outcomes. This stage aims to identify genetic characteristics associated with disease development, progression, or treatment response.

2.3. RadioGenomics Analysis. In oncological radiogenomics, feature selection precedes the development and assessment of predictive models. These models employ selected radiogenomic attributes to forecast specific clinical outcomes in cancer patients. Model performance is rigorously evaluated through metrics such as specificity, sensitivity, and AUC-ROC, often employing cross-validation techniques. Moreover, microarray gene expression studies are integral for linking gene profiles to imaging features specific to cancer.

In radiogenomics analysis, mathematical equations are used to model and study the relationships between radiomic features and genomic data. Here are some common mathematical equations and methods used in radiogenomics.

(i) Pearson's Correlation Coefficient: The degree and direction of a linear link between two continuous

variables is measured by the Pearson's correlation coefficient, such as a radiomic feature (X) and a genomic feature (Y). The equation (2.1) for Pearson's correlation coefficient is,

$$r = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}} \tag{2.1}$$

where n represents the number of data points (observations), $\sum$ denotes the summation sign, which means you need to sum up the values for all data points, X and Y are the two variables for which you are calculating the correlation coefficient (e.g., radiomic and genomic features), and X represents the mean of variable X, and represents the mean of variable Y.

(ii) Linear Regresssion: Linear regression models the relationship among the dependent variable (genomic feature) and one or more independent variables (radiomic features). The equation (2.2) for simple linear regression is:

$$Y = \beta_{\mathrm{D}} + \beta_1 X_i + \varepsilon_i \tag{2.2}$$

where Y is the genomic feature, β_0 and β_1 are the coefficients to be estimated, and X is the radiomic feature, and ϵ is the error term.

(iii) Machine Learning Algorithms: Complex interactions between radiomic and genomic variables are modelled using MI algorithms including random forests, SVM (support vector machines), and neural networks. The equations for these algorithms involve specific mathematical formulations to optimize model performance and predictions.

(iv) Cox Proportional Hazards Model: In survival analysis, the Cox proportional hazards model is commonly utilized for study the link among radiomic features and patient survival or time-to-event outcomes in the presence of other covariates. The equation (2.3) for the Cox model is,

$$h(t) = h_{\mathrm{Q(t)}} * \theta^{\sum x_i \beta_i} \tag{2.3}$$

where $h(t)$ represents the hazard function at time, t, $h_0(t)$ is the baseline hazard function, β are the coefficients for radiomic and genomic features, and patient survival or time-to-event outcomes in the Presence of other covariates, and X_i represents the corresponding feature values.
These are radiogenomics analysis mathematical tools. Based on the type of issues, datasets, and goals, additional machine learning and statistical methods can be used for radiogenomics analysis.

3. Review of Radiogenomis Studies. During this research, an extensive survey was done on various popular public databases, including PubMed and Google Scholar, and found that more than a thousand radiomics papers are reported in the PubMed/MEDLINE database between 2015 and 2023. The objective of this research endeavor is to provide a comprehensive survey of the existing literature pertaining to radiogenomics for various oncological disorders. Incorporating a multitude of oncological disorders in a radiogenomics review is instrumental for elucidating the complexity and multifaceted nature of this interdisciplinary field. Varied malignancies are characterized by unique genomic aberrations and radiomic phenotypes, thereby disease-specific research is required. For example, glioblastomas frequently exhibit IDH1 mutations, whereas breast carcinomas may be scrutinized for HER2 and BRCA1/2 aberrations. Such investigations result in various outcomes, including the development of predictive models, the identification of new biomarkers, and advancements in personalized treatments. The review encompasses a wide range of cancer types, offering a comprehensive view of radiogenomic science. It also demonstrates the versatility of these methods across different areas of cancer research. This approach involves thorough comparisons, critical evaluations of current methods, and discussions about new research ideas and future directions.

3.1. Brain. Radiogenomics primarily focuses on central nervous system disorders. Table 3.1 summarizes neuro-oncology. Microarray DNA data and GBM neuroimmune histochemistry are used to identify tumor gene expression non-invasively [22]. In the study, 82 treatment-naive subjects from The Cancer Genome Atlas related to radiography to semantic imaging [31]. Inflammation, edema, and cell proliferation genes and microRNAs were targeted. PERIOSTIN production, a marker associated with the subtype of GBM (p 0.0001), fast relapse,

and poor prognosis, has been linked to quantitative (the measuring of quantities inside tumor compartments) (p 0.001).

Mutations in IDH1 and IDH2 genes improve survival in glioma patients. Thus, doctors must be able to predict an IDH1 mutation before medication without harming the patient. The decision fusion architecture created by Chang et al. for MRI images used data from various institutions on glioblastoma stages I–IV. Grinband et al. used a conventional CNN approach based on segmented regions of interest (ROI) instead of Li et al.'s Hybrid architecture, which uses a convolutional network trained with patches of ROI, a fisher vector module for encoding salience maps, and a support vector machines classifier for estimating IDH1 mutation status. Inference on a multi-scale convolutional-only network produces feature maps represented by the fisher vector module, creating a compact representation like a bag of visual words. Multimodal low-grade glioma MRIs produced patches and ROIs. DenseNet architecture trained on multi-modal segmentations with 3D ROIs predicts IDH1 status.

DNA methylation error correcting MGMT condition. MGMT predicts GBM chemotherapeutic response. Prior work used a 50-layer ResNet, and a CNN trained on ROI data [44].

Low-grade gliomas with 1p19q co-deletion responded well to treatment and lived longer. A multi-kernel CNN [23] can predict 1p19q chromosomal expression in low-grade gliomas using T1- and T2-weighted MRI. The previous study [19] predicted the 1p19q deletion using the same deep architecture as IDH1 and MGMT. MRI texture can indicate a tumor's molecular subtype [13]. Classical (AUC=0.72) subgroups include pro-neural, mesenchymal, neural, and molecular. Radiomics effectiveness in identifying molecular subtypes encouraged the hunt for finer biological correlations. A field focused on predicting gene abnormalities used as biomarkers. T1 contrast and T2 FLAIR MR Image volumetric features linked with numerous well-known somatic mutations [43]. Mutations include TP53, RB1, NF1, EGFR, and PDGFRA. The first quantitative analysis used GBM "multiomics" data from TCGA, encompassing the transcriptome, proteome, and genome, and TCIA's matching images [15]. In a notable study, radiomic profiles were found to be associated with TP53, PTEN, and EGFR mutations [16]. The study employed random forest to discover multiple driver mutations (PDGFRA, EGFR, CDKN2A, PTEN, TP53, and RB1) based on multiparametric MRI characteristics, particularly from biopsy regions [17].

In studies of various brain tumors, including meningioma, radiomic features have been shown to group patients by grade (AUC=0.86; 81), phenotype (AUC=0.81; 81), or recurrence risk (AUC=0.72; p =0.28; 82). Neuroblastoma's genetic profile and medulloblastoma's molecular subtype were associated with semantics [20,21].

3.2. Lung. NSCLC (Non-Small Cell Lung Cancer) [40] accounts for 85% of lung cancer cases globally, with higher mortality rates. Thus, for early detection of lung cancer imaging (PET and CT) biomarkers are essential. Staging therapeutic options is challenging. EGFR (Epithelial Growth Factor Receptor) protein on cell surfaces is associated with malignancy. Predicting EGFR mutation profile can lead to improved and personalized treatments. Table 3.2 represents the review about the lung tumor [42].

EGFR is a cell surface protein that regulates cell growth and is commonly mutated in NSCLC. EGFR-targeted therapies like TKIs- Tyrosine Kinase Inhibitors are effective in treating EGFR-mutated NSCLC. KRAS-Kirsten Rat Sarcoma Viral Oncogene Homolog is a proto-oncogene linked to various cancers, including lung cancer, this is linked to a patient's treatment resistance. ALK- Anaplastic Lymphoma Kinase gene rearrangements are found in some patients of lung cancer, particularly non-smokers with adenocarcinoma, and are targeted by ALK inhibitors with remarkable efficacy. Understanding EGFR, KRAS, and ALK status is crucial for personalized lung cancer treatment, providing better outcomes with targeted therapies.

Radiomics is promising in predicting tumor genetic states, including ALK, EGFR, and KRAS [17]. KRAS shows prognostic value in various radiomic features. Effective therapeutic staging requires CT, PET scans, genetic, and laboratory biomarkers for personalized treatment decisions.

A CNN method was proposed, trained on CT patches/nodules marked by EGFR, offering non-invasive diagnostics, and supporting biopsy-identified mutations [29]. This study investigated deep-learning imaging characteristics related to NSCLC EGFR mutation status. A non-invasive investigation was used to confirm the mutational status determined by biopsy.

Genetic mutational status has become crucial in clinical decision-making for NSCLC since the FDA approved targeted therapy. NSCLC patients face challenging therapy decisions due to EGFR and KRAS muta-

tions' mutual exclusivity. KRAS mutation is a genetic alteration in the KRAS gene that leads to uncontrolled cell growth and is commonly associated with various cancers. Targeted therapies directed at these biomarkers have revolutionized lung cancer treatment, providing more effective and less toxic options for specific patient subgroups.

3.3. Breast and Ovaries. Since the 1970s, breast parenchyma has been studied for breast cancer risk assessment [31]. Recently, texture analysis distinguished low-risk wild-mutations from high-risk BRCA-mutations using AI methods [32]. Radiogenomics prediction models were further improved using Bayesian artificial neural networks and convoluted neural networks (AUC = 0.86) [34]. Interest in breast radiogenomics has expanded to include MRIs, with quantitative imaging linked to molecular subtypes [35]. Machine learning models recognized breast cancer characteristics, aiding risk assessment [32]. Ovarian cancer also benefits from molecular subtyping, guiding prognosis [37]. Radiogenomics holds promise for novel imaging markers with clinical potential [38]. Advancements in personalized cancer management are on the horizon. Table 3.3 represents the review of the Breast and Ovarian tumor.

The significance of molecular subtyping has also risen in the context of ovarian cancer. Accurate prognostic indicators are crucial for guiding clinical decisions, especially considering the high probability of recurrence in high-grade serous ovarian cancer [34]. Recognizing the value of merging subtype and survival gene expression patterns, researchers developed the "Classification of Ovarian Cancer" (CLO-VAR) prognostic model [36]. Semantic characteristics from a rare radiogenomic multicenter investigation involving 92 patients with high-grade serous ovarian cancer were found to be correlated with the CLOVAR system subtypes and progression time [38]. Epithelial ovarian cancer, with a 5-year survival rate ranging from 35% to 40%, necessitates precise patient categorization [39]. Radiogenomics provides insights into breast and ovarian cancer, offering novel imaging markers, enhancing personalized cancer management, and utilizing AI and machine learning, with promising potential for improved risk assessment and targeted treatments in cancer care [43].

3.4. Liver and colorectal carcinoma. Hepatocellular carcinoma (HCC) accounts for a significant proportion of early-stage liver cancer cases and is a leading cause of global cancer-related deaths. Fibroblast Growth Factor (FDFR) Receptor gene that has been implicated in liver cancer. These mutations may contribute to the development and progression of hepatocellular carcinoma, the most common type of primary liver cancer.

Radiogenomics research in HCC has evolved in two parallel lines, with one study using machine learning (ML) to accurately predict FDFR2 mutation in 89% of cases with a smaller sample size (n=33), demonstrating high specificity (94%) and sensitivity (87%). However, a preliminary investigation (n=66) utilizing semantic characteristics failed to detect any connection with the genetic mutation, emphasizing the need for improved prediction models through machine learning.

Colorectal cancer (CRC) is influenced by RAS gene family members that act as molecular "switches" controlling cell cycle proteins and transcription factors. KRAS mutations occur in 30-50% of CRC cases, while NRAS mutations are present in 3-5% of cases, and both are typically considered mutually exclusive. RAS mutations are associated with increased angiogenesis, cell proliferation, and metastatic potential and are used as prognostic biomarkers in the clinic, indicating EGFR antibody resistance, like NSCLC.

Various imaging techniques have been explored to develop predictive indicators for KRAS mutational status in CRC. Traditional radiomics revealed a link between KRAS mutations and skewness on CT images (p=0.02) [29]. More advanced machine learning classifiers have identified radiomics signals that predict NRAS (AUC is 0.686), BRAF (AUC is 0.857), and KRAS (AUC is 0.829) mutations with varying degrees of success. However, the lack of standardization across different tumor types hinders contrast of radiomic features associated with the similar mutation, emphasizing the need for tumor-independent radiogenomic characteristics using large datasets and advanced classification techniques.

Text-based strategies were developed to predict KRAS mutational status using descriptive language from radiology reports [26]. The trained classifier parsed radiology reports for mutant and wild-type samples, identifying specific words used more frequently for each category. The study found that KRAS-mutant tumors were often described as "few," "discrete," and "[no] recurring," while wild-type tumors were more frequently described as "multitude," "lobed," and "frequent." Further research in radiogenomics holds promise for improving cancer diagnosis and personalized treatment approaches [27]. Table 3.4 presents the review about the Liver and colorectal carcinoma.

Table 3.1: Overview of Radiogenomics methods for Brain tumor

Author	**Type of Lesion**	**Study of Gene**	**Type of analysis**	**Image Type**	**Software for feature extraction**	**Features Identified**	**Methods**	**Results**
Ziinn et. al. [13]	Gliomas	PERIOSTIN	Correlative analysis	T1 Contrast	Pyradiomics	Features of FLAIR volumes	Decision Trees	Shorter time to disease progression and Decreased survival (P<0.001)
Yang et. al. [15]	Gliomas	TP53	Correlative analysis	MRI-FLAIR	Matlab	Texture based features	Random Forest	Survival status is 0.72.
Czarnek et. al. [16]	Gliomas	POSTN	Predictive analysis	Flair MRI	Fourier Desciptor algorithm	Shape-based features	Machine Learning	Better Performance of the classification model with AUC > 0.5
Mazuriowski et al.[17]	Gliomas	EGFR, PIK3R1	Correlative analysis	MRI	matlab	Shape-based features	Machine Learning	Patient Survival rate (p=0.006)
Beig et. al. [23]	Gliomas	IDH1	Predictive analysis	T1 and T2 weighted	Matlab	First-order, shape-based features	Machine Learning	Patient Survival rate (p=0.003)
Rathore et. al. [24]	Gliomas	PIK3CA	Correlative analysis	T1 weighted and T2 weighted MRI	CapTk	Texture based features	K-Means Clustering	Categories of PTEN, TP53, EGFR genotype.
Hassan et. al. [18]	Gliomas	EGFR, PIK3R1	Correlative analysis	T1 weighted MRI	In-house radiomics pipeline	Texture based features	DNN	Patient Survival rate ($p < 0.001$)

3.5. Prostate and Rena Cell Carcinoma. Given that the clinical outcome of prostate cancer is connected closely to a primary tumor suppressor gene, radiogenomics, PTEN, has an effective promise in such cases. Table 3.5 represents the review of the prostrate and renal cell carcinoma. In Prostate cancer loss of PTEN is linked to increased mortality and clinically aggressive phenotype. Where multi-parametric MR scans fail in yielding any Correlated/predictive features [32], contrast uptake on T2-weighted image intensity skewness (p<=0.1), and DCE-MRI (p<0.01) is correlated with PTEN expression [30].

Radiogenomics studies were conducted on prostate cancer patients receiving MR-guided biopsies using a unique approach. Since the location of the biopsy was detected via a scan and the ROI was used for extracting radiomics features, a precise radiomics biological link could be established. This method was used to identify radiomics characteristics linked to predictive biomarkers [33,34].

The diagnosis of renal cell carcinoma (RCC) is now occurring at earlier stages, leading to more effective treatment options, primarily driven by the widespread adoption of colon cancer interventions, to reduce postoperative recurrence. The function in hypoxia signaling, Von Hippel Lindau (VHL) mutational status is frequently employed in the clinic as both a prognostic and predictive biomarker for RCC. It was shown that VHL mutations were significantly linked with nodular tumor enhancement (p=0.020), distinct tumor margins (p=0.013), and clear presence of intertumoral vascularity (p=0.018). Table 3.5 demonstrates that BAP1, PBRM1, and

Table 3.2: Overview of radiogenomics methods for lung tumor

Author	**Type of Lesion**	**Study of Gene**	**Type of analysis**	**Image Type**	**Software for feature extraction**	**Features Extracted**	**Methods**	**Results**
Gevaert et al. [12]	Lung tumor	EGFR	Predictive analysis	PET/CT	Matlab	Shape, edge, texturebased features	Linear regression	Better Performance of the classification model with AUC = 0.086
Sorensnet al.[13]	Lung tumor	EGFR	Predictive analysis	PET/CT	In-house computer algorithms	Edge, texture, shape based features	Classical Radiomics	EGFR mutation analysis with p = 0.05
Zhou et al. [14].	Lung tumor	KRAS	Correlative analysis	CT	matlab	Shape, Texture based features	Machine Learning	Association between phenotype and genotype
Moon et al. [15]	Lung tumor	KRAS	Correlative analysis	CT/PET	matlab	First order characteristics	Deep Learning	Pateint survival rate with progression p < 0.05
Kim et al. [16]	Lung tumor	EGFR	Correlative analysis	CT	In-line computer algorithms	Shape based features	Classical radiomics	EGFR mutation analysis with p = 0.04

VHL mutations could be detected with an accuracy of 0.75 with classifiers that use machine learning techniques validated on local datasets and tested on TCGA patients.

Radiogenomic research has focused on BAP1 mutation with VHL since it was demonstrated to be a substantial unfavorable prognostic indicator for patients with renal cell carcinoma, particularly when combined with a concurrent loss of PBRM1. To forecast the mutational status, Vikram et al, collected quantitative information from 78 cases renal cell carcinoma from the TCGA (pre-contrast AUC = 0.78) and discovered that BAP1-mutated RCCs tend to display the tumor margins (p = 0.002), CT renal vein invasion (p = 0.046) [36], and higher pathological Fuhrman grade score. Beyond specific genes, epigenetic correlations between DNA methylation in RCC and CT radiomic characteristics were also found.

4. Comprehensive insights from literature review: radiogenomic applications in diverse oncological conditions.

1. Breast Cancer: Radiogenomics shows promise in differentiating between BRCAmutated highrisk and lowrisk wildtype breast cancers. Advances in AIbased texture analysis and machine learning have significantly improved predictive modeling, facilitating personalized treatment.
2. Liver Cancer (Hepatocellular Carcinoma): Distinctive advancements in HCC radiogenomics have emerged, particularly using machine learning to predict FDFR2 mutation status with high accuracy. This offers significant potential for the development of targeted therapies.
3. Ovarian Cancer: Radiogenomics has been particularly relevant in ovarian cancer subtyping and prognostication. Leveraging large multicenter datasets and advanced classification techniques, researchers aim to identify tumor-independent radiogenomic markers for refined patient classification and treatment selection.
4. Lung Cancer: Deep learning techniques in radiogenomics have been effectively used to predict EGFR mutations in non-small cell lung cancer, thereby facilitating targeted therapies such as EGFR tyrosine

Table 3.3: Overview of radiogenomics methods for breast and ovarian cancer

Author	Type of Lesion	Study of Gene	Type of analysis	Imaging Type	Feature extraction method	Features Identified	Methods	Results
Li et al. [21]	Breast tumor	BRCA	Predictive	Mammogram	Matlab	Entropy, Tumor size, shape based features	Machine Learnng	AUC = 0.87
Li et. A1 [22]	Breast Tumor	BRCA	Predictive	mamogram	Computer algorithm	Volume, Area of tumor, size based features	Deep learning	AUC = 0.83
Grim m et.a1.,[24]	Breast Tumor	ER/PR/ HER2	Correlative	MRI	In-house computer algorithms	Second-order characteristics features	SVM classifier	Luminal B subtype classification
Mazorowski et. a1., [25]	Ovarian tumor	BRCA	Correlative	MRI	Radiomics tools	First order Features	Logistic regression	Classifier status =74 % , PR status =65 % HER2 =18 % .
Saha et. al [26]	Ovarian Tumor	HER2	Predictive	MRI	Radiomics tools	Tum or Texture, Area of Tumor, shape based features	Deep Learning	Luminal A AUC =0.697.

kinase inhibitors to improve patient outcomes.

5. Colorectal Cancer: Radiogenomics research has identified potential imaging markers for KRAS and NRAS mutational status, aiding in prognostic stratification and guiding treatment strategies.
6. Glioblastoma: Radiogenomics helps identify correlations with MGMT methylation status, enabling personalized treatment regimens including the use of alkylating agents.
7. Prostate Cancer: In prostate cancer, radiogenomics has identified MRI texture features correlating with PTEN gene deletion, informing risk stratification and treatment choices such as surgical intervention or active surveillance.
8. Methodological Advancements: Recent strides in integrative radiogenomics frameworks that combine traditional statistical methods with machine learning have increased both the robustness and predictive accuracy of the models.
9. Ethical and Regulatory Considerations: Issues such as patient consent, data sharing, and algorithmic transparency are gaining attention, calling for ethical guidelines and regulatory oversight for clinical adoption.
10. Clinical Translation and Validation: Despite advancements, direct clinical application remains nascent, requiring further large-scale, multi-center trials for validation and reliability assessment.

5. Limitation of Radiogenomics. Limitations are derived from literature review and expert consultations. Existing literature revealed gaps such as sample heterogeneity and algorithmic biases. Expert input confirmed these limitations and provided detailed insights into technical and ethical challenges. This dual approach ensures that the limitations mentioned are supported by academic foundations and validated through the opinions of current experts.

Table 3.4: Overview of radiogenomics methods for liver and colorectal carcinoma

Author	Type of Lesion	Study of Gene	Type of analysis	Image type	Feature extraction method	Features Extracted	Methods	Results
Kuo et al. [29]	Liver Tum or	TP53	Correlative	PET/CT	CapTk	Grey Level Mean, Maximum, Shape, etc.	Machine Leaming	Survival rate $p<0.05$
West et al. [28]	Liver Tumor	Metastasis TP53	Predictive	CT	Matlab	Shape, Tutmox size, area of the tutnot, Volum etric etc,	Classical Radiomics	Confirmed TP53 AUC is 86.61 %, Specificity is 92.31 %, Sensitivity is 92.9 %.
Lubner et a1. [30]	Colorectal Tumor	KRAS	Correlative	PET	Radiomics tools	First order character- istics	Machine Leaming	KRAS mutations were neg- atively associ- ated with Skewness (P=0.02).
Lovinfosse et al. [31]	Colorectal Tumor	KRAS	Correlative	CT	Matlab tools	Grey Level Mean Maximum, Shape etc.	Deep Leaming	Eighty- three patients had RAS mutations: 9 NRAS, 74 KRAS and and 68 pa- tients had no changes.

Limited sample sizes: Some radiogenomics studies may have small sample sizes, which can limit the generalizability of the findings.

Data heterogeneity: Variability in imaging protocols and equipment across different institutions can introduce heterogeneity in radiomic data, affecting the consistency of results.

Retrospective data: Many radiogenomics studies rely on retrospective data, which may lead to selection bias and other limitations in study design.

Standardization challenges: Lack of standardized radiomic features and methodologies can make it difficult to compare results across different studies.

Overfitting: Complex machine learning algorithms used in radiogenomics may lead to overfitting, where the model performs well on training data but poorly on new data.

6. Application of Radiogenomics. Radiogenomics, the integrated study of radiomic and genomic data, has been increasingly recognized for its potential in oncology. The literature reveals extensive applications of radiogenomics in predicting treatment responses, distinguishing aggressive phenotypes, identifying genomic alterations, and determining tumor heterogeneity. Moreover, its utility extends to predicting patient prognosis, facilitating the understanding of potential metastatic risks, and aiding in the selection of suitable therapeutic strategies. These advancements highlight the transformative potential of radiogenomics in tailoring precision medicine approaches, underscoring its significant role in enhancing diagnostic and therapeutic decisions.

Survival Analysis. Conceptual Framework: Survival analysis in radiogenomics seeks to correlate radiomic features extracted from medical images with genomic profiles to predict patient outcomes, such as overall survival or disease-free survival.

Table 3.5: Overview Of Radiogenomics Methods For Prostate Cancer And Renal Cell Carcinoma

Author	Type of Lesion	Study of Gene	Type of analysis	Imaging type	Feature extraction method	Features Extracted	Methods	Results
Vander Weele et a1.[32]	Prostrate tumor	PTEN	Correlative	MRI	In-house computer algorithms	Shape, Texture, edge etc.	Machine Learning	Feature values with expressions less than 0.25 and interquartile ranges (IQRs) less than 0.5 were filtered for significant representation
Mc Cann et al. [33]	Prostrate tumor	PTEN	Predictive	MRI	CapTk	Edge, texture, shape.	Classical Radiomics	Binary classification of prostate cancer.
Stoyanova et a1. [33, 34]	Prostrate tumor	General gene expression	Correlative	MRI	Matlab	Shape, Texture	Machine Learning	Identification of prostrate tumor
Shinagare et a1.[36]	Rena1 tumor	BAP1	Correlative	CT	In-house computer algorithms	First order characteristics	Deep Learning	Correlation between BAP1 and features for Renal tumor.
Karlo et a1. [37]	Renal tumor	PBRM1, VHL	Correlative	MRI	In-house computer algorithms	Nodular tumor	Classical radiomics	Correlation between PBRM1 and features for Renal tumor.

A commonly used model is the Cox Proportional Hazards Model is calculated in equation (6.1),

$$h(t \mid X) = h_0(t) \exp\left(\beta_1 x_1 + \beta_2 0 x_2 + \cdots \beta_y x_0\right) \tag{6.1}$$

Here, $h(t \mid X)$ is the hazard function dependent on time t and covariates X, and $h_0(t)$ is the baseline hazard.

Figure 6.1 depicts a Kaplan-Meier survival curve, which is commonly used in medical research to represent the fraction of patients living for a certain amount of time after treatment. Kaplan-Meier survival curve, extracted from a comprehensive literature review, showcases the survival probabilities of high-risk and low-risk patient cohorts over time. Its strength lies in adeptly representing censored data and enabling direct comparisons between groups. The curve's trajectory reveals significant survival differences between the cohorts, supported by the provided p-value. Kaplan-Meier's visual clarity ensures its widespread use in oncology research, offering immediate insights for experts and practitioners.

Figure 6.1 has been adapted to vividly illustrate survival probabilities over a 12-year span [41]. The X-axis marks time in years, while the Y-axis denotes survival probability from 0 to 1. The high-risk group, represented

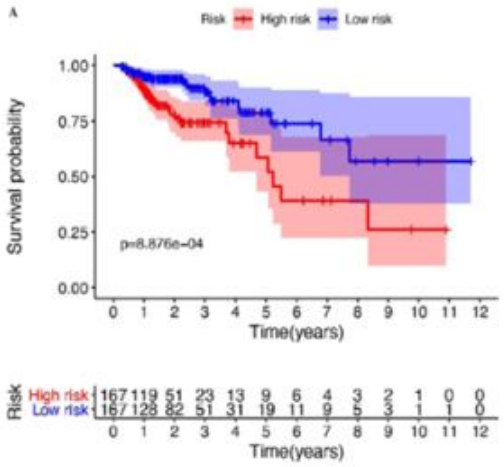

Fig. 6.1: Comparative Kaplan-Meier Survival Analysis of High-risk vs. Low-risk Patient Cohorts

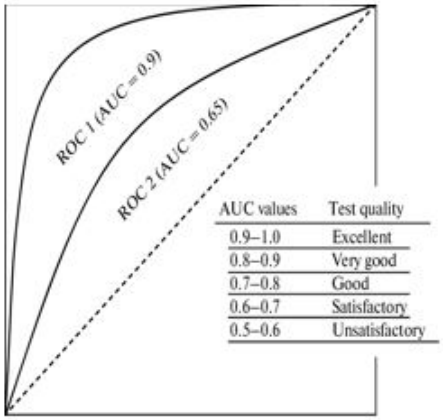

Fig. 6.2: Evaluation of Diagnostic Test Performance: ROC Curves and AUC Value Interpretation for Metastasis Prediction

by the red curve, showcases a steeper decline in survival compared to the blue curve of the low-risk group. At year 0, both cohorts start near a 1.0 survival probability, but by year 12, the high-risk group approaches 0.25 while the low risk remains above 0.5. Cross marks indicate censored data points, where exact survival times are unknown. The significant p-value of 8.876e-04 emphasizes the meaningful difference between these two groups. The risk table below provides a numerical breakdown of patients remaining in each cohort over the years.

Predicting Metastasis. Conceptual Framework: Radiogenomics can predict the likelihood of metastasis by linking image-derived radiomic features with genomic markers known to be associated with metastatic spread.

Logistic regression can model this binary outcome is calculated as in equation (6.2),

$$\log\left(\frac{g}{1-\eta}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 \cdots\cdots \tag{6.2}$$

Here, p represents the probability of metastasis occurring

The depicted diagram, Figure 6.2, showcases two Receiver Operating Characteristic (ROC) curves, instru-

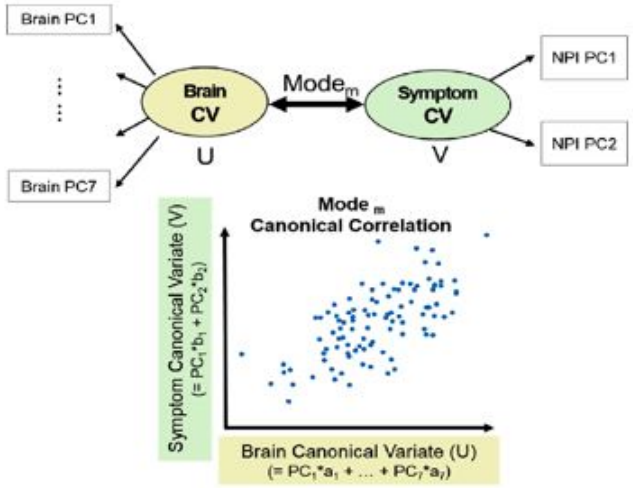

Fig. 6.3: Canonical Correlation Analysis between Brain Principal Components and Symptom Severity

mental in evaluating the performance of diagnostic tests, especially in predicting conditions like metastasis in oncology [34]. The ROC curve, as illustrated in Figure 6.2, is a graphical representation of the true positive rate (sensitivity) against the false positive rate (1-specificity) for various threshold values. A perfect diagnostic test would result in a curve passing through the top-left corner, indicating 100% sensitivity and 100% specificity.

Within Figure 6.2, two ROC curves are displayed: ROC1 with an Area Under the Curve (AUC) of 0.9 and ROC2 with an AUC of 0.65. AUC is a metric capturing the overall performance of a diagnostic test, ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). Here, ROC1, boasting an AUC of 0.9, denotes "Very Good" test quality, implying a high accuracy in predicting metastasis. In contrast, ROC2, also presented in Figure 6.2, with an AUC of 0.65 signifies just a "Satisfactory" test quality. The accompanying table within Figure 6.2 provides a categorical assessment of AUC values, guiding interpretations of test efficacies.

Integrative Approaches. For simultaneous analysis of radiomic and genomic data, Canonical Correlation Analysis (CCA) is often used shown in equation (6.3)

$$\text{Maximize}\, u^T X v \tag{6.3}$$

Here u and v are weight vectors for the radiomic and genomic datasets, and X is the correlation matrix.

Figure 6.3 depicts a graphical representation of the canonical correlation analysis, a statistical method utilized to ascertain the relationship between two sets of variables [39]. In this case, the two sets are the principal components (PCs) derived from brain data (Brain PC1 to Brain PC7) and the principal components from symptom data (NPI PC1 and NPI PC2). The purpose of canonical correlation is to find pairs of linear combinations, one from each set, that have maximum correlation with each other.

In the depicted Figure 6.3, these linear combinations are referred to as "Brain CV" (canonical variate U) and "Symptom CV" (canonical variate V). The scatter plot showcases the canonical correlation for a specific mode (Mode m), plotting the relationship between the Brain Canonical Variate and the Symptom Canonical Variate. As indicated by the equations at the bottom, each canonical variate is a linear combination of its respective PCs, weighted by certain coefficients (a's for the brain). Visualization aids in discerning the strength and nature of the relationship between the brain's structural features and symptom severity, offering invaluable insights into potential neurological underpinnings of the presented symptoms.

7. Conclusion and Future work. In this comprehensive review, the salient advancements, and challenges in the domain of radiogenomics research are highlighted, especially in the context of various oncological disorders. Radiogenomics, grounded in earlier research, is still an emerging field. Despite the existing challenges, significant progress has been made in understanding and addressing various tumor types. The advent

of deep learning and advanced artificial intelligence techniques in medicine shows potential in navigating the current barriers in the practical utilization of radiogenomics.

As the horizon unfolds, the integration of these cutting-edge technologies is expected to redefine the clinical paradigm in radiogenomics. This transformative shift calls for radiologists to adapt and actively immerse themselves in the innovations. The ongoing growth of this interdisciplinary realm will likely lead to more tailored therapeutic approaches for cancer care, emphasizing the imperative for future studies to refine and standardize these burgeoning methods.

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