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Review

Multi-omics synergy in oncology: Unraveling the complex interplay of radiomic, genoproteomic, and pathological data

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ABSTRACT

The advent of multi-omics approaches has revolutionized the field of oncology by enabling a comprehensive understanding of cancer biology through the integration of diverse biological data. This review aims to explore the synergy between three key omics domains: radiomics, genoproteomics, and pathomics. Radiomics involves extracting high-dimensional data from medical images, providing valuable insights into tumor heterogeneity and treatment response. Genoproteomics, encompassing both genomic and proteomic analyses, delves into the molecular mechanisms driving cancer progression and therapeutic resistance. Pathomics leverages advanced digital pathology techniques to quantitatively analyze tissue architecture and cellular morphology. We provide an in-depth overview of the methodologies and tools employed in each omics field, highlighting their specific applications in oncology, including cancer diagnosis, biomarker discovery, and prediction of treatment outcomes. Furthermore, we discuss the integration of multi-omics data, addressing the challenges and innovative solutions for harmonizing these complex datasets. Through an examination of recent advancements and case studies, we underscore the critical role of multi-omics in advancing our understanding of cancer and paving the way for more effective and personalized therapeutic strategies.

1. Introduction

The concept of "omics" originated primarily from the field of genomics, which studies the entire genome rather than just function and expression of individual genes.[1] Advancements in high-throughput sequencing technologies and large-scale parallel techniques, such as mass spectrometry, have spurred the rapid development of various omics fields, including genomics, proteomics, pathomics, transcriptomics, metabolomics, single-cell transcriptomics, and single-cell multi-omics.[2]

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Today, multi-omics technologies are leading the way in biomedical research.[3,4] These approaches enable researchers to gain a detailed understanding of the roles of genes, proteins, metabolites, and biological pathways in disease occurrence and progression.[5] For instance, in the field of oncology, multi-omics approaches have revolutionized our understanding of cancer biology. With multi-omics technologies, researchers can systematically acquire molecular information across biological levels, thereby obtaining an overall view of tumor behavior. This has led to important insights into critical factors such as tumor evolution, tumor heterogeneity, and the tumor microenvironment, promoting the development of precision cancer treatments.[6]

Moreover, the application of various omics technologies reveals underlying disease causes and the complex biological interactions between primary causes and functional consequences.[7] Multi-omics technologies are also crucial for advancing personalized precision medicine. By leveraging multi-omics data, the accuracy of clinical diagnostic algorithms can be improved, thereby reducing the occurrence of missed and incorrect diagnoses.[8] Multi-omics analyses are also valuable in predicting disease and understanding its potential mechanisms. Such analyses are increasingly central to the development of treatment strategies tailored to the unique biological characteristics of each individual.[9] Furthermore, multi-omics technology plays a crucial part in assessing treatment response and monitoring disease progression. The integration of multi-omics data enables researchers to predict cancer patients' responses to treatments such as chemotherapy and radiotherapy and monitor patients' responses to drug treatments during the course of disease therapy, supporting clinical decision-making and helping to optimize treatment plans.[10,11]

This review highlights the integration and application of multi-omics technologies in oncology, focusing on radiomics, genoproteomics, and pathomics. The specific objectives include summarizing the main methods and techniques, highlighting the applications of these omics technologies in cancer research, and discussing the challenges faced in current research as well as future research directions. Through this comprehensive overview, we aim to address current gaps in the field of multi-omics knowledge and support advancements in cancer research and treatment.

2. Radiomics

2.1. Overview of radiomics

Radiomics, first proposed by Lambin et al.[12] in 2012, has developed rapidly. The initial objective was to utilize advanced automated or semi-automated techniques to quantify features in medical images, such as computed tomography (CT) or magnetic resonance imaging (MRI) scans, transforming the images into extractable data and identifying correlations with clinical metrics (e.g., tumor subtypes and prognosis). Unlike traditional imaging diagnostics, radiomics allows for noninvasive quantification of phenotypic characteristics and microenvironments on a broad scale, providing a quantitative description that addresses spatial and temporal heterogeneity, which has drawn substantial interest in clinical oncology research.[13] With technological progress in deep learning algorithms, the predictive performance of radiomics models has improved significantly, providing valuable support for decision-making in precision medicine.[14]

2.2. Techniques and methods in radiomics

In the field of radiomics, research can be subdivided into different focus areas based on the type of imaging data or research methods used. However, the overall research approach generally involves the following key stages: data collection, image preprocessing, region of interest (ROI) segmentation, feature extraction and selection, model construction, and performance evaluation.

2.2.1. Data collection

Establishing inclusion and exclusion criteria that align with clinical needs and guidelines, as well as collecting a sufficiently large set of medical images and clinical data are fundamental to radiomics research. The lax inclusion criteria can lead to bias, reducing the reference value of studies and the applicability of models. However, constructing large-scale datasets is costly. Organizations such as the Cancer Imaging Archive (TCIA)[15] and Quantitative Imaging Biomarkers Alliance[16] are promoting the development of public databases that researchers can use for model pretraining and generalization performance testing.

2.2.2. Image preprocessing

Variations in imaging parameters, such as pixel size, slice thickness, and noise, can lead to variability in radiomic features.[17] Additionally, motion artifacts due to movement, detector malfunctions, or bones and metal implants can alter images. To enhance model stability, preprocessing steps, such as denoising, interpolation, and intensity normalization, must be tailored to the specific imaging modality. While classic interpolation algorithms are still widely used, new algorithms are continually being developed. For instance, generative adversarial network–based algorithms can learn the mapping relationships of image representations across different imaging devices and parameters, enabling the adjustment of test set images to have feature distributions similar to those of the target dataset.[18]

2.2.3. ROI segmentation

Accurately defining the ROI is a critical step in radiomics research, which requires consistent segmentation of tumors and related tissue regions. Most clinical tasks still rely on manual or guided segmentation schemes, especially when the shape of the lesion is irregular or the boundaries are blurred. Automatic segmentation techniques are still being explored.[19]

Feature Extraction and Selection: Radiomics quantifies imaging phenotypes into feature values using predefined formulas and deep learning networks. Predefined features, such as shape, histogram, and texture, must adhere to standardized guidelines, such as

the Image Biomarker Standardization Initiative,[20] to ensure reproducibility. Deep learning models extract features using multilayer neural network structures, typically based on convolutional neural networks (CNNs) or vision transformers. Extracted features must be normalized, and those with poor reproducibility or redundancy should be removed. Such removal is commonly performed using the intraclass correlation coefficient, coefficient of variation, and Bland–Altman plots. Additionally, techniques such as ComBat[21] can be employed to adjust feature values and mitigate batch effects.

2.2.4. Model construction

Common radiomics tasks involve classification (e.g., subtype prediction, tumor metastasis, gene mutation) and survival prediction (e.g., overall survival [OS], progression-free survival). Radiomics utilizes machine learning models, including regression analysis, Bayesian networks, support vector machines (SVMs), random forests, and deep learning networks, to identify associations between radiomic features and clinical indicators. The model output can be combined with qualitative semantic features, demographic data, and clinical test indicators to enhance predictive accuracy and practicality. When selecting models and setting hyperparameters, it is crucial to strike a balance between learning ability and overfitting risk. Complex models, while capable of learning more associations, are more prone to overfitting. Methods for preventing overfitting include carefully setting hyperparameters, cross-validation, regularization, early stopping, and data augmentation. Deep learning networks have been widely used in recent years to construct high-performance radiomics models, but their effectiveness typically relies on experience and optimization. Automated strategies, such as network architecture search,[22] offer alternative design approaches. Additionally, strategies like online learning and distributed learning have been developed to handle continuous patient enrollment and improve privacy protection.

2.2.5. Performance evaluation

External test sets, cross-validation, and subgroup analysis help gauge model generalizability across different patient distributions and imaging parameters. Clinical applicability should be tested on large-scale prospective multicenter datasets registered on platforms, ClinicalTrials.gov for example, to obtain reliable evaluations from low-bias populations. Common performance evaluation metrics include accuracy, sensitivity, specificity, receiver operating characteristic curves, calibration curves, decision curves, the Kappa index, and Kaplan–Meier curves. Interpretability and uncertainty are crucial to deep learning models, which can be enhanced through activation maps and dimensionality-reduction methods, such as t-distributed Stochastic Neighbor Embedding. Statistical tests should employ methods such as Bonferroni correction to avoid false positives. Additionally, the clinical significance of the model needs to be compared with existing clinical indicators and guideline-recommended diagnostic schemes. Moreover, to increase research reproducibility, it is recommended to prioritize open-source programming platforms, function packages, and software, and to disclose the software versions and code that have been employed.

Radiomics has shown great promise in improving diagnostics, prognosis assessment, and treatment prediction, significantly enhancing clinical workflows, and supporting precision medicine, all of which ultimately benefit patients. Typical applications of radiomics in clinical oncology are summarized in Table 1.

2.3. Applications in oncology

In 2016, Huang et al.[31] conducted a landmark study using radiomics to predict lymph node metastasis (LNM) in colorectal cancer. They employed the least absolute shrinkage and selection operator (LASSO) along with logistic regression for feature selection and developed a predictive model integrating the radiomics signature, clinical indicators, and radiologist-reported metastasis status. This model improved preoperative prediction of metastasis, with an area under the curve (AUC) of 0.778. In 2018, Sun et al.[32] were the first to utilize radiomics to predict immunotherapy responses by developing a model based on PET/CT image analysis. The model demonstrated impressive performance (AUC > 0.8), underscoring the promising potential of radiomics in the context of tumor immunotherapy. Dong et al.[33] proposed a deep learning–based feature-extraction algorithm for the task of predicting the number of LNMs in gastric cancer cases. By adding regularization terms to the feature extraction layer, performing correlation analysis to select key convolutional layer nodes, and using various statistical formulas to evaluate feature maps, they reduced feature redundancy and increased extraction efficiency. Their study demonstrated that combining radiomics with deep learning enhances the model's accuracy when handling complex data. Additionally, radiomics has been applied to various essential diagnostic tasks, such as differentiating between benign and malignant tumors,[23] subtype classification,[24,34] local progression,[25] and distant metastasis.[26,27]

Table 1
Radiomics studies in clinical oncology.

Authors (Year)	Type of task	Image Modality	Modeling	Evaluation
Saha et al. (2024)[23]	Detection	MRI	Ensemble learning	AUC: 0.91
Li et al. (2023)[24]	Lauren classification	Dual-energy CT	Random forest	AUC: 0.802
Pan et al. (2023)[25]	T4 stage	CT	ResNet and machine learning	AUC: 0.950
Dong et al. (2019)[26]	LNM	CT	DenseNet and machine learning	C-index: 0.797
Liu et al. (2024)[27]	Extranodal soft tissue metastasis	CT	ResNet and logistic regression	AUC: 0.761
Jiang et al. (2021)[28]	Survival	CT	S-net	C-index: 0.792–0.802
Liu et al. (2019)[29]	pCR to NAC	Multiparametric MRI	SVM and logistic regression	AUC: 0.86
Jin et al. (2021)[30]	pCR to NACR	Longitudinal MRI	Siamese network	AUC: 0.97

Radiomics also shows great potential in prognosis and treatment response prediction. Typically, regression labels combined with follow-up time and censoring status are used for prognosis, while treatment response is encoded as classification labels. In 2014, Aerts et al.[35] extracted over 1200 radiomic features from CT images of patients with non-small cell lung cancer (NSCLC), successfully predicting patient prognosis and survival outcomes. This study, as the first large-scale research in the field of radiomics, demonstrated the link between imaging features and tumor heterogeneity and biological behavior. Subsequently, Wang et al.[36] and Zhang et al.[37] used radiomics to predict prognoses of esophageal cancer and gastric cancers, integrating deep learning and predefined features with clinical indicators. Jiang et al.[28] applied the S-net network structure to integrate multilevel deep features at multiple levels, expanding the level range of prognostic feature extraction. Predicting treatment response enables timely treatment adjustments. For example, patients with a predicted pathologic complete response (pCR) might avoid surgery and preserve their organs, while those predicted to be unresponsive to neoadjuvant therapy could switch to alternative treatments in a timely manner to reduce toxicity. Liu et al.[29] constructed a prediction model for pCR to neoadjuvant chemotherapy (NAC) using radiomic features extracted from multiparametric MRI, achieving a significantly higher AUC than the clinical model. Jin et al.[30] created a multitask deep learning framework based on a Siamese network architecture, which incorporates multi-timepoint dynamic information. This model achieved an AUC of 14 %–19 % greater than models trained using single-timepoint images for predicting pCR in neoadjuvant chemoradiotherapy (NACR).

2.4. Challenges in applying radiomics to oncology

Despite its potential, the application of radiomics to oncology still faces several challenges. For example, radiomics research requires large, high-quality datasets, but acquiring such datasets in practical research is challenging. Additionally, the "black box" nature of deep learning and issues with reproducibility hinder the clinical translation of radiomics.[38] Nevertheless, with the continuous increase in effective training sample sizes and significant improvements in hardware and software performance, researchers are now combining advanced artificial intelligence (AI) techniques, such as foundational models and diffusion models, to construct more predictive tools. These advancements deepen the impact of radiomics and create new opportunities in precision medicine, boosting both diagnostics and therapeutic guidance for clinicians.

3. Genomics and proteomics

3.1. Overview of genomics and proteomics

Genomics is the study of all the genes within an organism and their functions, with a focus on gene structure, function, and interactions.[39] The origins of genomics trace back to 1953, when James D. Watson and Francis Crick discovered the double helix structure of DNA—a significant breakthrough that transformed biological science.[40] This discovery spurred advancements in DNA sequencing technologies,[41] laying the foundation for genomics. With the Human Genome Project, initiated in 1990 and completed in 2003, genomics has evolved rapidly, becoming an effective research tool for addressing rare and common genetic diseases and cancers, thereby greatly promoting the fields of medicine and biology.[42]

The development of genomics has also fueled progress in related fields, such as proteomics, which studies all proteins within a cell or organism, including their expression, functions, and interactions.[43] Since proteins catalyze and control virtually all cellular processes, a comprehensive and quantitative understanding of the proteome, including its structure, function, and dynamics, has long been a crucial aspect of biological research. However, achieving a comprehensive exploration of the proteome remains a major challenge in the current development of proteomics. This challenge has been partially addressed by the continuous development of mass spectrometry, which enables the reliable measurement of most proteins and has led to a period of rapid development in proteomics.[44] Leveraging the functional characteristics of proteins, proteomics offers significant advantages in exploring how genetic and nongenetic risk factors correlate with clinical outcomes, identifying new drug targets, and translating biomarkers, which provides valuable insights into cellular functions and disease mechanisms.[45]

3.2. Techniques and methods in genomics and proteomics

The development and application of genomics are heavily reliant on high-throughput sequencing technology, which has evolved in three stages. The first was marked by the development of Sanger sequencing, which enabled the decoding of entire genome sequences. The second stage saw the advent of next-generation sequencing (NGS), which improved upon the high cost and slow pace of Sanger sequencing, significantly enhancing sequencing speed, cost, and accuracy and allowing large-scale genomic studies. However, NGS has limitations, particular the shorter read lengths (typically 100–300 base pairs), making it challenging to resolve complex genome repeat sequences and structural variations. Additionally, NGS requires polymerase chain reaction (PCR) amplification, which can introduce biases and errors. The third stage involved the emergence of third-generation sequencing, which produces much longer read lengths, ranging from several thousand to tens of thousands of base pairs, thus addressing the issues of complex genome repeat sequences and structural variations without relying on PCR amplification, thereby reducing amplification-induced biases and errors. Both second- and third-generation sequencing technologies are now widely used and have considerably advanced genomic research.[46,47] Furthermore, genome editing technologies such as CRISPR-Cas9 play a crucial role in genomic research. CRISPR-Cas9 allows researchers to precisely modify and manipulate specific genes to control gene expression and induce epigenetic changes, greatly advancing gene function studies and gene therapy.[48,49]

Proteomics research relies on key technologies such as mass spectrometry (MS) and protein microarrays. MS, which is central to protein identification and quantification, includes methods such as liquid chromatography-tandem mass spectrometry and matrix-assisted laser desorption/ionization time-of-flight/time-of-flight. These techniques allow systematic identification and localization of modified amino acids within polypeptide chains, determination of subunit composition, stoichiometry, topology of multiprotein complexes, and analysis of three-dimensional structures.[50] MS further supports the simultaneous measurement of the absolute or relative abundance of thousands of proteins, offering high throughput and sensitivity.[51] In contrast, protein microarray technology centers on detecting protein expression and various interactions, such as protein–DNA, protein–RNA, protein–protein, and protein–drug. Protein microarrays allow the analysis of thousands of proteins in a single experiment, greatly advancing the study of protein functions and interactions. By providing high-throughput screening, rapid analysis, and low sample consumption, this technology is a vital tool in proteomics research.[52,53]

3.3. Applications of genomics and proteomics in oncology

Genomics and proteomics are essential in oncology research by not only helping scientists decipher the molecular mechanisms of tumors but also advancing personalized medicine and precision treatments. Typical applications of genomics and proteomics in clinical oncology are summarized in Table 2.

3.3.1. Biomarker discovery

A key application of genomics and proteomics in oncology research is the identification of tumor biomarkers. Proteins serve as critical indicators for studying the relationship between human health and disease. By combining genomics and proteomics, researchers can identify biomarkers closely associated with the occurrence and development of cancer and potential targets for future targeted therapies, providing a basis for early diagnosis and personalized treatment.[60] For example, Sun et al.[54] utilized plasma proteomics data from seven large-scale genome-wide association studies and employed the Mendelian randomization analysis to identify 13 proteins significantly associated with colorectal cancer (CRC) risk. They confirmed shared causal variants between these proteins and CRC risk through colocalization and summary-data-based Mendelian randomization (SMR) analysis. Additionally, by analyzing protein interactions, they identified four proteins with potential as therapeutic targets for CRC. Similarly, Bertucci et al.[55] found significantly higher mutation frequencies in nine driver genes, including TP53, ESR1, and GATA3, in early-stage breast cancer. Detecting the status of these genes can provide reliable evidence supporting the early identification and selection of patients needing clinical trial treatments.

3.3.2. Personalized medicine

In the field of personalized medicine, the application of genomics and proteomics has greatly improved the precision of cancer treatments. Integrative analysis of genomic and proteomic data enables personalized treatment based on the specific genetic or protein expression profiles of patients, markedly improving therapeutic outcomes. Li et al.[56] conducted comprehensive genomic and proteomic analyses of metastatic CRC patients, identifying common gene mutations and signaling pathway abnormalities, such as KRAS, and profiling protein expression profiles and phosphorylation patterns under different mutation statuses. This research identified several potential therapeutic targets, providing precise molecular targets for personalized treatment and assisting clinicians in formulating individualized treatment strategies to improve therapeutic efficacy. In another study, Dong et al.[57] successfully identified FGFR2 fusion genes and associated phosphorylation sites in their proteogenomic characterization of intrahepatic cholangiocarcinoma patients. They determined the protein and phosphoprotein expression profiles under different mutation statuses, revealing the molecular mechanisms of various mutations and fusion genes, providing a reliable scientific basis for personalized treatment.

3.3.3. Treatment response evaluation

Another crucial application of genomics and proteomics in oncology research is the evaluation of treatment response. By integrating genomic and proteomic data, researchers can predict patients' responses to treatments such as chemotherapy and immunotherapy, aiding physicians in optimizing treatment plans. For example, Knisbacher et al.[58] conducted whole-genome sequencing, transcriptome sequencing, and proteomic analysis of acute myeloid leukemia (AML) patients, revealing the molecular landscape of CLL. They identified various mutations and gene expression changes related to disease progression and prognosis, as well as leukemia-associated protein modifications and several potential prognostic molecular markers. These prognostic markers can help predict AML patients' survival rates and disease progression risks, assisting clinicians in devising more precise treatment plans, thus improving therapeutic outcomes and patient quality of life. Similarly, Zhang et al.[59] developed a prognostic model based on EMT-related gene signatures to predict survival in CRC patients. Collectively, these studies demonstrate that the integration and analysis of multi-omics data can significantly enhance the precision of prognosis evaluation and treatment planning for cancer patients.

3.4. Challenges in the application of genomics and proteomics to oncology

Despite their transformative impact, several challenges remain for genomics and proteomics in oncology. First, cancer exhibits complex genetic characteristics. Additionally, the genetic material obtained from tumor samples during clinical treatment is often limited, which may result in the loss of somatic mutation signals and affect detection sensitivity. Preservation methods for tumor samples may lead to DNA damage, resulting in false-positive outcomes. The use of NGS algorithms also requires a trade-off between sequencing breadth, depth, and throughput to obtain the most comprehensive information possible.[61]

Table 2
Genomics and proteomics studies in clinical oncology.

Author (Year)	Task	Data Type	Research Methods	Results
Sun et al. (2023)[54]	Biomarker identification	Protein quantitative trait loci	Mendelian randomization analysis, colocalization analysis, SMR analysis, HEIDI test, single-cell RNA sequencing analysis	Decreased levels of 11 proteins, including CLSTN3, were associated with increased CRC risk, with SMR test $P < 0.01$
Bertucci et al. (2019)[55]	Genomic characterization	Whole-exome sequencing	Mutation analysis and clonal diversity assessment	Identified mutations in 9 driver genes (29 % mutation rate in TP53, 22 % in ESR1, etc.), TP53 mutation HR = 2.20, $P < 0.001$
Li et al. (2020)[56]	Proteogenomics study	Genomics, proteomics, phosphoproteomics	Proteomics and phosphoproteomics analysis	Identified phosphoproteomic profiles distinguishing metastatic from non-metastatic CRC, accurately predicting drug response
Dong et al. (2022)[57]	Proteogenomics study	Proteomics, phosphoproteomics, genomics, transcriptomics	Proteomics and phosphoproteomics analysis	Identified 4 iCCA subgroups, determined multiple driver gene mutations and significant prognostic markers
Knisbacher et al. (2022)[58]	CLL profiling study	Genomics, transcriptomics, epigenomics	Multivariate analysis	Identified 202 candidate driver genes, improved prognostic models, enhancing FFS and OS prediction accuracy
Zhang et al. (2020)[59]	Prognostic prediction	RNA sequencing	Cox proportional hazards analysis, LASSO regression analysis	High EMT risk scores were associated with shorter OS, AUC > 0.8

Abbreviations: 1. CLL: chronic lymphocytic leukemia 2. HEIDI: Heterogeneity in Dependent Instruments 3. CRC: colorectal cancer 4. HR: hormone receptor 5. FFS: Failure-free survival 6. EMT: epithelial-mesenchymal transition

In the field of proteomics, challenges include a lack of standardization in data analysis methods and the complexity of interpreting public datasets, which often lack essential clinical outcome information for clinicians' use and interpretation. Consequently, many proteomics research findings remain in the academic realm and are not immediately applicable to clinical practice.[62]

4. Pathomics

4.1. Overview of pathomics

Pathomics represents a pivotal component of multi-omics approaches in oncology,[63,64] focusing on the detailed analysis of disease pathology through advanced imaging and computational techniques.[65] The integration of whole-slide imaging (WSI) and AI has revolutionized the field, enabling the extraction of high-dimensional data from histopathological slides.[66] This synergy enhances our understanding of tumor biology, facilitates accurate diagnoses, and informs personalized treatment strategies.[67,68] For instance, both the Virchow and Prov-GigaPath models were established using WSI.[69,70] Virchow, one of the largest foundational models in computational pathology, is trained on 1.5 million H&E-stained WSI images from approximately 100,000 patients, supporting tasks such as pan-cancer detection and biomarker prediction.[69] However, current studies have yet to fully exploit WSI, as most pathology models only sample portions of WSIs, which may result in the omission of critical information. In response to this issue, Vorontsov et al.[70] developed the Prov-GigaPath model, which employed a GigaPath architecture that integrated a patch encoder and a slide encoder to capture both local and global image features, enabling the analysis of ultra-large WSI and providing more comprehensive information.

WSI involves the digitization of entire histological slides, allowing pathologists to analyze tissue samples at a microscopic level using digital tools.[71,72] Coupled with AI and machine learning algorithms, WSI enables the automated extraction and analysis of complex histological features, bridging the gap between conventional pathology and molecular data.[65,73]

4.2. Methods and tools in pathomics

4.2.1. WSI

WSI technology digitizes histological slides at high resolution, producing detailed images that can be analyzed computationally.[74] Moreover, digitization allows for the preservation, sharing, and reanalysis of pathological data. Key components of WSI systems include high-resolution scanners, image storage solutions, and specialized software for viewing and annotating digital slides.[75]

4.2.2. AI and machine learning

AI, particularly machine learning and deep learning algorithms, plays a key part in analyzing WSI data.[76] These algorithms are trained on large datasets of annotated histopathological images to recognize patterns and features associated with different cancer types and stages.[77–81] Technoloogies including CNNs and large language models (LLMs) have proven especially effective in image analysis tasks, including tumor detection,[80] classification,[82] and segmentation.[83] LLMs address the limitations of existing AI tools, which primarily focus on visual processing while overlooking natural language understanding. Lu et al.[84] developed a multimodal generative pathology AI assistant named PathChat based on LLMs and visual encoders. PathChat leverages the Llama 2 model to effectively incorporate natural language capabilities into medical applications, demonstrating excellent performance (89.5 % accuracy) across various pathology tasks.

Advanced image analysis software, often incorporating AI algorithms, is essential for extracting meaningful data from WSIs. These tools can quantify features such as nuclear morphology, cellular density, and tissue architecture, providing quantitative metrics that correlate with molecular and clinical outcomes. Examples of such software include ImageJ,[85] QuPath,[86] and the lifelines toolkit.[87]

4.3. Applications in oncology

The application of WSI and AI in pathomics has transformative potential in various aspects of oncology, including diagnosis,[78,88–91] prognosis,[92] and personalized treatment, which are summarized in Table 3.

4.3.1. Diagnosis

AI-enhanced WSI improves diagnostic accuracy by automating the detection and classification of tumors.[78] Algorithms trained on large datasets can identify subtle histopathological features that may be overlooked by human pathologists.[88] For example, AI models can distinguish between benign and malignant lesions,[93] identify cancer subtypes,[91] and detect metastases in lymph nodes with high precision.[80] This automation reduces diagnostic variability and supports pathologists in making accurate and consistent diagnoses.[67]

4.3.2. Prognosis

Prognostic assessments benefit from the quantitative analysis of histopathological features using WSI and AI.[94] Machine learning models can analyze features such as tumor-infiltrating lymphocytes,[95] mitotic figures,[93] and necrosis[84] to predict patient outcomes. For example, studies have shown that the density and spatial distribution of immune cells within tumors, quantified through digital pathology, are correlated with survival rates and responses to immunotherapy.[94] These prognostic biomarkers enable the stratification of patients into risk categories to guide treatment decisions.

Table 3
Pathomics studies in clinical oncology.

Author (Year)	Application	Data	Modeling	Performance
Lu et al. (2021)[90]	Benign and malignant diagnosis	H&E-stained WSI	Weakly supervised deep learning network	AUC = 0.921–0.991
Woerl et al. (2020)[91]	Subtype identification	H&E-stained WSI	Weakly supervised convolutional neural network	AUC = 0.76–0.89
Wu et al. (2023)[80]	Metastases prediction	H&E-stained WSI	Deep convolutional neural network	AUC = 0.906–0.998
Bai et al. (2021)[95]	Prognosis prediction	H&E-stained WSI	Machine learning	$P < 0.01$
Shi et al. (2021)[94]	Prognosis prediction	H&E-stained WSI	Weakly supervised deep learning framework	$P < 0.0001$

4.3.3. Therapeutic targeting and personalized medicine

The use of WSI and AI in pathomics aids in the identification therapeutic targets by linking histopathological features with molecular data.[96] AI algorithms can uncover patterns in tissue morphology that correlate with specific genetic mutations or protein expressions, suggesting potential therapeutic targets.[97] For instance, the presence of certain histological patterns indicating actionable mutations such as epidermal growth factor receptor (EGFR)[98] or anaplastic lymphoma kinase (ALK)[99] in lung cancer can inform the use of targeted therapies. Personalized treatment strategies can thus be based on comprehensive analysis of both morphological and molecular data.

4.3.4. Understanding the tumor microenvironment

The tumor microenvironment (TME) plays a crucial role in cancer progression and therapy response.[100] WSI and AI enable detailed characterization of the TME by quantifying the presence and spatial organization of various cell types, including immune cells, fibroblasts, and blood vessels.[96,98,101,102] This information provides insights into the interactions between tumor cells and their microenvironment, informing the development of strategies to modulate the TME and strengthen therapeutic efficacy. For example, the density of tumor-infiltrating lymphocytes, quantified through digital pathology, has been linked to the efficacy of immune checkpoint inhibitors.[103,104]

4.4. Challenges in pathomics for oncology applications

Similarly, there are several challenges in the development of pathology. Variations in slide preparation, staining, and the use of different data scanners can affect research reliability. Moreover, most whole-slide digital scanners are only capable of generating two-dimensional planar images, meaning that their ability to capture depth information is limited.[105] Nevertheless, overall, the integration of WSI and AI into pathomics offers unprecedented opportunities to advance our understanding of cancer biology and improve clinical outcomes. By leveraging high-resolution digital images and sophisticated AI algorithms, this approach enhances diagnostic precision, prognostic assessments, and personalized treatment strategies. As technology evolves, the interactions among WSI, AI, and other omics disciplines will further unravel the complexities of cancer, paving the way for innovative therapeutic interventions and personalized oncology.

5. Integration of multi-omics data

5.1. Methods and tools for multi-omics data integration

The development of AI technologies, including radiomics, enables the prediction of tumor pathology subtypes, molecular biomarker status, and individualized prognoses. However, the high-dimensional image features extracted by AI models are relatively abstract, the biological mechanism is still unclear, and the interpretability of the features is poor. In recent years, researchers have used radiogenomic analysis to explain the biological significance of image features extracted by AI models and to establish the link between macroscopic images and microscopic biological mechanisms. For instance, Grossmann et al.[106] predicted lung cancer prognosis using CT images and explained the biological meaning of CT-derived image features through radiogenomic analysis. In their study, tumor regions were manually delineated from the CT images of 262 lung cancer patients, and 636 radiomic features were then extracted from the tumor region images. Moreover, for gene sequencing data, gene pathways were first identified through gene enrichment analysis, and then the correlations between radiomic features and gene pathways were determined using bidirectional clustering: 13 gene modules were found, in which 210 radiomic features were significantly associated with 206 gene pathways. Different gene modules contained different radiomic features and the corresponding gene pathways that were significantly associated with these radiomic features; in some modules, the radiomic features (e.g., texture entropy, clustering features, and intensity change features) were associated with gene pathways related to the immune system or cell cycle regulation, the P53 pathway, and the transforming growth factor receptor beta signaling pathway. Other gene modules contained radiomic features that were associated with mitochondrial pathways as well as with transcription, translation, and RNA regulatory mechanisms.

Similarly, Sun et al.[107] used MRI images and RNA sequencing data to conduct image–gene multi-omics analyses, exploring the association between image features extracted by AI models and microscopic biological processes. The researchers collected multi-parameter MRI images (T1, T2, T2-FLAIR, and T1-enhanced sequences) and analyzed the OS data for 198 patients with glioma. For 95 of these patients, RNA-sequencing information was also available. First, a physician delineated the tumor lesion, including its parenchymal and peritumoral regions, on the patient's multiparametric MRI images. Then, the PyRadiomics toolkit was used to extract a total of 1032 radiomic features, such as shape, intensity, and texture, from the tumor parenchymal, peritumoral edema, and entire tumor areas of the four MRI sequences. In this dataset, data from 132 patients were used in the training set, and data from 66 patients were used as the validation set. In the training set, repeatability verification, univariate tests (*P*-value), and LASSO feature screening were performed on the radiomic features. Finally, the LASSO–Cox model was constructed to predict the OS of glioma patients with the screened radiomic features.

For the radiogenomics dataset, the highly interconnected genes were clustered into several gene modules that participate in common biological processes through weighted gene coexpression network analysis. Z-summary statistics were used to test the reproducibility of each gene module in both the radiogenomics dataset and the Cancer Genome Atlas (TCGA) datasets (159 patients) and to screen out reproducible gene modules (z-summary $\geq$ 10). Finally, gene modules significantly associated with radiomics signatures (predicted values of radiomics models) were identified through sample-based gene-set variation analysis. For each gene module, gene pathway enrichment analysis was used to determine whether each gene pathway in the gene module is significantly correlated with the radiomics signature. Each radiomic feature with a prognostic value was significantly correlated with a gene pathway. To further verify whether the image–gene correspondence found in this dataset is stable and reproducible, an external testing set (78 patients) was used for validation.[107] Finally, 13 radiomic features were screened, and the constructed radiomics model had a C-index of 0.7 in predicting the OS of glioma patients in the internal validation set. For the radiogenomics dataset, 27 gene modules were screened, 23 of which were found to be stable and reproducible in TCGA dataset. Two gene modules were significantly correlated with the radiomics score: one contained genes related to immunity, inflammation, and cell proliferation, and the other contained genes related to cell signaling pathways. Thirty genes in these two gene modules were found to have significant correlation with 13 radiomic features with prognostic value. Compared with previous studies that only constructed radiomics models to predict the prognosis of glioma, this study demonstrated the underlying biological mechanisms of radiomic features through image–gene multi-omics analysis.[107] Itakura et al.[108] also conducted an image–gene multi-omics study to predict glioma prognosis, using RNA pathway analysis to explain biological mechanisms of image-based radiomic features.

Wang et al.[109] also used radiogenomics methods to examine the association between radiomic features and microscopic gene pathways related to targeted lung cancer targeted therapy. The authors presented a deep learning model for whole-lung analysis. Without manually annotating CT images, the fully automated deep learning model was able to extract whole-lung features and predict EGFR gene mutation status in lung cancer. The model contained 768-dimensional deep learning features extracted from whole-lung CT images, and 29 prognostic features that could predict the progression-free survival of lung cancer patients receiving EGFR-targeted therapy were identified. In TCIA dataset, including CT images and RNA sequencing data for 87 patients, the researchers first extracted 29 image features with prognostic value for each patient using the whole-lung deep learning model. Next, they examined the associations between each gene pathway and the image features through gene enrichment analysis. Four image features were found to be significantly associated with four gene pathways. Two of these features were related to the ERBB and P53 signaling pathways, which were associated with the drug resistance mechanism in targeted therapy. The other two image features were related to the cell adhesion molecule pathway and extracellular matrix receptor interaction pathway, which were associated with cancer metastasis. These results suggest that image features extracted from whole lungs have prognostic value, providing microscopic information related to targeted therapy resistance and cancer progression mechanisms.

Recently, Vanguri et al.[110] adopted a combination of CT and histopathologic images along with gene data to predict the response to anti-programmed death-1/programmed death-ligand 1 (PD-L1) therapy among NSCLC patients. When extracting CT features, they annotated all the lesions in lung parenchymal, pleural, and lymph nodes for all the patients and extracted 1688 radiomic features using the PyRadiomics toolkit. Then, they selected stable radiomic features with small robustness z-scores indicating segmentation perturbation. The authors extracted histopathological features from PD-L1 immunohistochemistry-stained images, and HALO AI software (a deep learning model) was used to segment tumor areas in the images; then, 150 gray level co-occurrence matrix texture features were extracted from tumor areas in the images. All the patients underwent next-generation tumor sequencing prior to the start of treatment. Genomic alterations in genes commonly associated with NSCLC and thought to be associated with anti-PD-L1 therapy response (e.g., EGFR, ALK, ROS1, RET, HER2/ERBB2, BRAF and MET) were extracted from the cBioPortal as genomic features.

Finally, the authors proposed a multimodal dynamic attention with masking model combining multimodal features to predict immunotherapy responses in NSCLC patients. The model was based on a multiple-instance learning paradigm, with an attention layer to enhance important features among the three modalities: CT images, histopathological images, and genomic data. The model achieved an AUC of 0.8, outperforming the tumor mutation burden index (AUC = 0.61) and PD-L1 immunohistochemistry score (AUC = 0.73). The multimodal model also outperformed all tested unimodal models (AUC = 0.65 for the CT model, AUC = 0.73 for the IHC model, and AUC = 0.66 for the genomic model), indicating the importance of utilizing multimodal data in predicting NSCLC prognosis and treatment response.

5.2. Challenges in multi-omics integration applications

Radiogenomics research is crucial for enhancing the interpretability of AI models and image features. Researchers are increasingly integrating genetic information to explain the biological mechanisms underlying image features and AI models, which may help clinicians

to better understand AI outputs and the biological significance of high-dimensional image features. However, most radiogenomics studies follow similar analytical processes, such as extracting features from multimodal data and combining them to build diagnostic or prognostic models or conducting correlation analyses to link gene pathways and image features. These studies may face some key challenges. First, the high cost of acquiring multi-omics data (e.g., histopathological images and gene sequencing) often limits the size of the dataset, which may reduce the generalizability of findings. Second, different AI models produce different image features, leading to varied outcomes. Effective image features rely heavily on specific training datasets. Changes in training data can alter feature selection, which have impacts on results. For instance, using different deep learning models to extract features or using different datasets may select different image features, and the multi-omics analysis may yield different image–gene correlations.

Future studies should prioritize large datasets and test multiple AI models for image feature extraction in multi-omics analyses, with the aim of identifying stable correlations across diverse data modalities.

6. Challenges and prospects

In the field of oncology, radiomics is a crucial branch of precision medicine that reveals tumor microstructures by extracting detailed features from medical images. However, to fully realize its potential, we must address and overcome a series of challenges.

6.1. Data quality and standardization issues

High-quality, extensive, and diverse datasets are essential for developing robust radiomics models. Additionally, data quality, standardization, and data sharing are crucial issues in using radiomics in tumor research.

First, variability in image acquisition is a key challenge in radiomics. The quality and characteristics of medical images often vary due to differences in equipment, institutions, and parameter settings, making the consistent extraction of tumor features difficult.[111] Therefore, it is crucial to strictly document and standardize image acquisition parameters to ensure the comparability of image data obtained under different conditions.[112] Additionally, the diversity of equipment and parameter settings may affect the distribution of feature measurements, increasing the complexity of radiomic analysis.[113]

Second, issues related to data formats and sharing are also pivotal. Currently, clinical imaging data are predominantly siloed within individual medical institutions, lacking a unified platform for sharing. In tumor radiomics research, standardized data formats are a prerequisite for multicenter studies and data sharing.[114] Despite widespread resource limitations, cultural and language differences, issues with data recording methods, and legal privacy concerns,[115] the use of centralized data collection methods, such as the American Society of Clinical Oncology, can facilitate widespread data sharing while ensuring data privacy.[116]

To achieve widespread clinical implementation of radiomics, it is essential to address the challenges of image acquisition standardization and data sharing. By establishing unified image acquisition protocols and promoting cross-institutional and international data-sharing mechanisms, we can build a more robust foundation for the precise diagnosis and treatment of tumors.

6.2. Ethical and privacy concerns

Due to the rapid development of medical imaging technologies and data analysis methods, tumor radiomics has demonstrated great potential in improving the efficiency of disease diagnosis and treatment. However, progress in this field has also raised privacy and ethical concerns.[117] For instance, there is a risk of revealing patients' sensitive personal information through data analysis, and big data analysis may lead to privacy breaches.[118] There are several key aspects of radiomics research and applications that must be addressed to protect patient privacy and ensure that ethical standards are upheld, which are described below.

Medical imaging data contain personal biometric information, requiring strict privacy protection measures. Data deidentification and access control are fundamental to protecting patient privacy. For example, research has shown that reversible data hiding using contrast enhancement in medical images, in combination with plain-text encryption, can protect the privacy of medical imaging data while increasing image quality.[119]

While interinstitutional data sharing can promote scientific development, it also carries the risk of privacy breaches. Secure data transmission and sharing technologies, such as blockchain and secure multiparty computation, are crucial for mitigating these risks. For example, a privacy-preserving medical image-sharing method using deep sparse transform learning and obfuscation was shown to protect image data while allowing authorized users to reconstruct images using neural autoencoders and sparse transformation.[120]

In the context of the Internet of medical things, conventional encryption methods may not be suitable due to processing limitations. To address this issue, a medical imaging privacy protection data model using visual cryptography (VC) was developed to store biomedical data in different databases; it employs transfer learning to optimize neural networks, thereby mitigating the performance degradation caused by the noise introduced by VC.[121]

The development of machine learning models for medical imaging analysis necessitates the consideration of privacy protection within the design phase. The use of enhanced detectors on the client side, integrated with contextual information, has been shown to support effective medical imaging analysis while ensuring the protection of privacy.[122]

Another issue relates to sharing medical images and information. To securely share medical images among different centers, it is imperative to utilize a data-sharing mechanism that incorporates privacy protection. One such innovative mechanism has been proposed; it stores medical images in an encoded and obfuscated format while providing authorized users with private keys that can be used to reconstruct the images.[123] It is crucial to use a privacy system that considers the legal, regulatory, managerial, and technological issues related to sharing personal medical data.

In the era of big data, addressing the challenges of sharing and privacy protection for personal medical data has become a systematic engineering challenge, underscoring the importance of establishing robust legal regulations and ethical reviews to safeguard patient privacy.[118] Moreover, obtaining informed consent is a critical component of medical imaging research. It is essential that patients fully understand the purposes and modalities of their data usage and provide voluntary informed consent based on this understanding.[124] Meeting these standards is not only an ethical obligation but also a legal necessity to foster public trust and ensure the integrity of medical research. Through the implementation of these measures, we can advance medical imaging research, including radiomics, while safeguarding the rights and privacy of research participants.

To address these challenges and ensure the protection of patients' rights and the maintenance of public trust in medical research, a multifaceted approach must be adopted. Implementing a series of measures to protect privacy and ethics will allow us to stimulate scientific progress while ensuring the security of patient data and adherence to ethical standards for research.

6.3. Future research opportunities and directions

Multimodal radiomics, which employs the same lesion across different imaging modalities or comparative analysis methods, integrates various imaging modalities, such as CT, MRI, and PET, along with genomic and other biological data, employing the same lesion for comparative analysis. This approach provides a comprehensive description of tumor phenotypic features and deepens our understanding of the complex relationships between tumor imaging characteristics and the underlying biological processes. Consequently, it increases the accuracy of tumor diagnosis and prognosis. For example, multi-omics analysis can reveal the role of γδ T cells in improving the TME, the efficacy of immunotherapy, and the prognosis of cervical cancer.[125]

Current radiomic analyses depend on images reconstructed from signals collected by imaging equipment, which can lead to the loss of critical diagnostic information for tumor diagnosis during the reconstruction process. Future research should concentrate on the direct analysis of raw signals obtained from imaging devices to create more direct diagnostic mapping models, thereby improving the accuracy and performance of tumor diagnostics.[126,127]

As the accuracy and stability of tumor auxiliary diagnostic models continue to improve, the interpretability of these models has become increasingly important. Enhancing model interpretability is essential for increasing clinical acceptance and the applicability of imaging biomarkers. Radiomics models based on feature engineering typically adopt simple, interpretable pattern recognition models with clear structures. Integrating prior knowledge into feature construction—such as characteristics indicative of tumor angiogenesis and vascular tortuosity—can help elucidate the physiological significance of the model.[128] However, radiomics models based on deep learning, despite their strong predictive capabilities, often lack interpretability. To address this, researchers are employing post hoc explanation methods, such as activation maximization and deconvolution, which use visualization techniques to highlight regions of the image that contribute to the predictive outcome.[129]

The development of radiomics systems that can assist clinicians in making tumor treatment decisions represents a key research direction. Applications of radiomics-based clinical decision support systems, such as IBM Watson, Viz.ai, and Lunit INSIGHT, which have received approval from the U.S. Food and Drug Administration, comply with the European CE marking, or are registered with National Medical Products Administration of China, have been applied in clinical practice to some extent. These systems help physicians make more accurate diagnoses and treatment decisions. For instance, in adaptive radiotherapy, treatment doses can be adjusted according to observed changes in the tumor region, offering a personalized approach to cancer treatment. Unlike static radiotherapy plans, adaptive radiotherapy requires ongoing assessment and adjustment, which may be guided by radiomics models that evaluate functional changes in the tumor area. This method is expected to promote patient outcomes by personalizing the radiotherapy process.

Future research should prioritize effective data integration and analysis while enhancing the transparency and credibility of models to achieve precise tumor diagnosis and treatment.

7. Conclusions

In this review, we comprehensively explored the latest advancements and applications of multi-omics research in oncology, focusing on radiomics, genoproteomics, and pathomics. By systematically integrating these omics data, we can gain new insights into tumor development, progression, and treatment. Radiomics extracts a vast array of features from imaging data, providing deep insights into tumor morphology and structure and thus enhancing the precision of tumor diagnosis and treatment response prediction. The integration of genomics and proteomics enables the identification of cancer-related biomarkers, providing a critical basis for personalized therapy and the development of new therapeutic approaches. Pathomics employs advanced microscopy techniques and data analysis tools to reveal the complexities of the TME and its interactions with the host, thus playing a crucial role in molecular subtyping and prognosis evaluation.

The application of multi-omics methods signifies a new era in oncology research. This approach not only enhances our understanding of tumor biology but also significantly advances oncology in several key areas, including precision medicine, early diagnosis and prognosis evaluation, and novel therapeutic strategies. By integrating various omics data, multi-omics methods can be used to tailor treatment plans for individual patients, substantially improving treatment efficacy and reducing adverse effects. Research grounded in multi-omics reveals new molecular targets, which provides essential directions for new drug development and therapeutic strategies.

CRediT authorship contribution statement

J. T: Supervision, Project administration, Conceptualization. **Y. L:** Writing – original draft, Investigation. **Y. L. L:** Writing – original draft, Validation, Investigation. **M. J. F:** Writing – review & editing, Project administration. **S. W:** Writing – review & editing, Supervision, Project administration. **L. Z. S:** Writing – review & editing, Validation, Formal analysis, Data curation. **R. Y. Z:** Visualization, Resources, Investigation. **D. D:** Supervision, Project administration, Conceptualization. **J. W. W:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Z. Y. L:** Supervision, Project administration, Conceptualization.

Declaration of Competing Interest

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