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RESEARCH

Radiogenomics in Sarcoma: Linking Imaging Features with Molecular Signatures for Precision Medicine

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ABSTRACT

Sarcomas are a rare and diverse group of malignant tumors that arise from mesenchymal tissues and exhibit significant genetic and biological heterogeneity. This complexity makes accurate diagnosis, prognosis, and treatment planning challenging. Radiogenomics, an emerging field that integrates medical imaging with genomic and molecular data, offers a non-invasive approach to better understand tumor biology. By correlating imaging features from modalities such as MRI and CT with molecular alterations, radiogenomics can improve tumor characterization, predict treatment response, and support personalized therapeutic decisions. This review summarizes recent advances in sarcoma radiogenomics, highlights its clinical applications, discusses current challenges, and explores its potential to enhance precision medicine through more accurate and individualized patient care.

Keywords: Sarcoma, Radiogenomics, Precision Medicine, Imaging Biomarkers, Genomic Signatures, Artificial Intelligence, Non-invasive Diagnosis**.**

INTRODUCTION

Sarcomas are a rare and diverse group of malignant tumors that originate from mesenchymal tissues, including bone, cartilage, muscle, adipose tissue, blood vessels, and other connective tissues. Although they account for less than 1% of adult malignancies, they represent approximately 15–20% of pediatric cancers, making them an important group of tumors in children and adolescents. Their marked histological, genetic, and molecular heterogeneity contributes to variable clinical behavior, creating significant challenges in diagnosis, prognosis, and treatment.(1,2)

Based on their tissue of origin, sarcomas are broadly classified into bone sarcomas and soft tissue sarcomas (STSs), with more than 80 recognized histological subtypes. The most common primary bone sarcomas include osteosarcoma, Ewing sarcoma, and chondrosarcoma, whereas frequently encountered soft tissue sarcomas include liposarcoma, leiomyosarcoma, synovial sarcoma, and undifferentiated pleomorphic sarcoma. Each subtype is associated with distinct molecular alterations that influence tumor development, metastatic potential, and response to therapy, emphasizing the need for subtype-specific diagnostic and therapeutic strategies.(3)

Soft Tissue Sarcomas

Soft tissue sarcomas are uncommon malignant neoplasms arising from non-osseous connective tissues such as adipose tissue, skeletal and smooth muscle, fibrous tissue, peripheral nerves, and blood vessels (Figure 1). They most commonly occur in the extremities, followed by the retroperitoneum, trunk, and the head and neck region. More than 70 histological subtypes have been identified, reflecting the remarkable biological diversity of these tumors.(4)

Accurate pre-treatment evaluation, including tumor grading and staging, plays a critical role in clinical management. These assessments provide valuable prognostic information and help guide treatment decisions involving surgery, radiotherapy, chemotherapy, or multimodal approaches. The molecular landscape of soft tissue sarcomas is equally diverse. Many subtypes harbor characteristic genetic abnormalities that serve as important diagnostic and prognostic biomarkers. For example, synovial sarcoma is defined by the SS18–SSX gene fusion, well-differentiated and dedifferentiated liposarcomas frequently exhibit MDM2 amplification, and gastrointestinal stromal tumors (GISTs) commonly contain activating mutations in KIT or PDGFRA. The identification of these molecular alterations has improved diagnostic accuracy and facilitated the development of targeted therapies, supporting a more personalized approach to sarcoma management.(5, 6)

Bone sarcomas are primary malignant tumors that develop from bone- or cartilage-forming tissues (Figure 2). Although uncommon, they are clinically important because they predominantly affect children, adolescents, and young adults. These tumors most frequently arise in the long bones, particularly the femur, tibia, and humerus, but they can also occur in the pelvis and spine.

The three major subtypes of bone sarcoma are osteosarcoma, Ewing sarcoma,

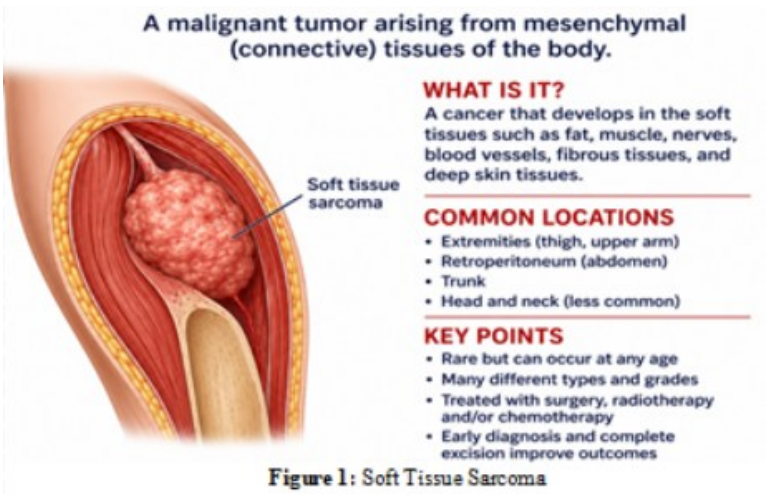

Figure 1: Soft Tissue Sarcoma

and chondrosarcoma. Osteosarcoma is the most common primary malignant bone tumor in adolescents and young adults and is characterized by the formation of malignant osteoid. Ewing sarcoma is a highly aggressive small round cell tumor that mainly affects children and young adults and is commonly associated with the EWSR1–FLI1 gene fusion. Chondrosarcoma primarily occurs in adults and originates from cartilage-producing cells, with conventional, dedifferentiated, and mesenchymal variants representing its major subtypes.

The molecular characteristics of bone sarcomas vary according to subtype. EWSR1 gene rearrangements are a hallmark of Ewing sarcoma, whereas mutations in IDH1 and IDH2 are frequently observed in central chondrosarcoma. Osteosarcoma commonly exhibits complex genomic abnormalities involving tumor suppressor genes such as TP53 and RB1, contributing to its aggressive biological behavior.

Clinical Challenges in Sarcoma

The clinical management of sarcoma remains challenging due to its marked histological and molecular diversity. Many sarcomas remain clinically silent until they reach an advanced stage, delaying diagnosis and treatment. In addition, obtaining representative biopsy samples can be difficult because of the deep anatomical location and heterogeneous nature of these tumors. These challenges underscore the need for accurate, non-invasive diagnostic tools and personalized treatment strategies that account for the unique biological characteristics of each sarcoma subtype.(7, 3)

Importance of Precision Medicine in Cancer Care

Conventional cancer treatment has traditionally relied on tumor histology, anatomical location, and disease stage to guide clinical decision-making. While this approach has improved patient outcomes, it often fails to account for the considerable molecular diversity that exists within tumors. Sarcomas, in particular, comprise numerous histological subtypes with distinct genetic alterations and clinical behaviors, making standardized treatment strategies less effective. Precision medicine seeks to overcome these limitations by tailoring diagnosis and therapy according to the molecular and genetic characteristics of individual tumors. In sarcoma, this personalized approach has the potential to improve diagnostic accuracy, predict treatment response, identify patients who may benefit from targeted or immunotherapies, and ultimately enhance clinical outcomes.(8)

Radiogenomics in Sarcoma

The complex biological and molecular heterogeneity of sarcomas makes them an ideal candidate for radiogenomic research. Although imaging techniques provide essential anatomical and functional information, they cannot fully reveal the molecular mechanisms driving tumor behavior. Conversely, genomic analysis offers detailed molecular insights but is dependent on tissue sampling, which may not accurately represent the entire tumor because of intratumoral heterogeneity. Radiogenomics combines the strengths of both approaches by linking imaging features with molecular signatures, enabling non-invasive prediction of genetic alterations, tumor aggressiveness, prognosis, and treatment response. Furthermore, recent advances in artificial intelligence (AI) and machine learning (ML) have significantly enhanced radiogenomic analysis by enabling automated feature extraction, pattern recognition, and predictive modeling, thereby supporting more precise and personalized management of sarcoma patients.(9)

This review provides a comprehensive overview of the current role of radiogenomics in the management of bone and soft tissue sarcomas. It summarizes recent advances in imaging-genomic correlations, outlines the radiogenomic workflow from image acquisition to data integration, and discusses current clinical applications and emerging evidence. The review also examines the major challenges limiting clinical implementation, including issues related to data standardization, reproducibility, and validation, while highlighting future opportunities involving artificial intelligence, deep learning, and multi-omics integration. By synthesizing the available evidence, this review aims to demonstrate how radiogenomics can bridge conventional imaging and molecular diagnostics, supporting the development of precision medicine for patients with sarcoma.

FUNDAMENTALS OF RADIOGENOMICS

Radiomics and Quantitative Imaging Features

Radiomics is an advanced image analysis technique that transforms conventional medical images into quantitative data, enabling objective assessment of tumor characteristics beyond visual interpretation. By extracting a large number of computational features from imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), radiomics provides valuable information about tumor phenotype and biological behavior.

The extracted features are generally categorized into three main groups. Shape -based features describe the geometric characteristics of a tumor, including its size, volume, surface area, and margins, which may reflect tumor growth and invasiveness. First-order or intensity features quantify the distribution of voxel intensities within the lesion, providing information about tissue composition,

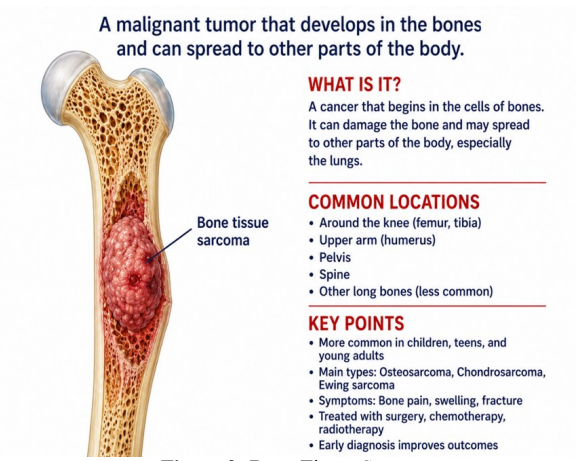

Figure 2: Bone Tissue Sarcoma

cellularity, and vascularity. Texture features evaluate the spatial arrangement and variation of pixel intensities, allowing assessment of intratumoral heterogeneity associated with necrosis, fibrosis, angiogenesis, and cellular density. Together, these quantitative imaging biomarkers enable comprehensive, non-invasive characterization of tumors and have become an important component of precision oncology.

Genomic Landscape of Sarcoma

Sarcomas exhibit remarkable genetic diversity, with distinct molecular alterations underlying their development and clinical behavior. Consequently, modern sarcoma classification increasingly incorporates molecular and genomic characteristics alongside conventional histopathological evaluation. Several recurrent genetic abnormalities are closely associated with specific sarcoma subtypes. For example, the EWSR1–FLI1 gene fusion is the defining molecular hallmark of Ewing sarcoma, whereas amplification of MDM2 is commonly observed in well-differentiated and dedifferentiated liposarcomas. Osteosarcoma frequently demonstrates complex genomic alterations involving tumor suppressor genes such as TP53, RB1, and ATRX, which contribute to tumor progression and therapeutic resistance. In addition to genetic mutations and chromosomal rearrangements, gene expression profiles and epigenetic modifications have emerged as valuable biomarkers for predicting prognosis and treatment response. The widespread adoption of next-generation sequencing (NGS) and other high-throughput genomic technologies has substantially improved our understanding of the molecular landscape of sarcomas, providing a strong foundation for radiogenomic investigations.(10)

Workflow of Radiogenomic Analysis

Radiogenomic analysis involves a systematic workflow that integrates medical imaging, quantitative image analysis, genomic profiling, and predictive modeling to characterize tumor biology and support precision medicine (Figure 4).

a. Image Acquisition

The first step involves acquiring high-quality medical images using standardized imaging protocols. The most commonly employed modalities include computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). CT provides excellent visualization of bone structures and tissue calcification, MRI offers superior soft tissue contrast and detailed anatomical information, while PET evaluates tumor metabolism and functional activity. Consistent image acquisition parameters are essential to ensure reliable feature extraction and improve the reproducibility of radiogenomic studies.(11)

b. Image Segmentation and Feature Extraction

Following image acquisition, the tumor is identified and segmented either manually, semi-automatically, or automatically to define the region of interest. Quantitative radiomic features are then extracted using specialized software. These features describe various tumor characteristics, including morphology, intensity distribution, texture, and spatial heterogeneity. Because hundreds or even thousands of features can be generated, feature selection methods and machine learning algorithms are subsequently applied to identify the most informative and biologically relevant parameters while minimizing redundancy.(12)

c. Integration with Genomic Data

The selected imaging features are subsequently correlated with molecular information obtained from tissue samples, including gene mutations, gene expression profiles, chromosomal alterations, and epigenetic modifications. Statistical analyses and computational methods are employed to identify meaningful associations between imaging phenotypes and underlying genomic signatures. This integration enables non-invasive prediction of molecular characteristics that are traditionally determined through tissue biopsy.(13)

d. Predictive Modeling and Clinical Application

The final stage involves developing predictive models using artificial intelligence (AI) and machine learning (ML) techniques. By integrating radiomic and genomic data, these models can predict clinically relevant outcomes such as tumor subtype, molecular profile, treatment response, risk of recurrence, and patient survival. Such predictive frameworks provide valuable decision-support tools that facilitate personalized treatment planning and advance the implementation of precision medicine in sarcoma management (Figure 4).(14)

MOLECULAR LANDSCAPE OF SARCOMAS

Common Genetic Alterations in Major Sarcoma Subtypes

a. Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor and predominantly affects adolescents and young adults. It is characterized by extensive genomic instability and numerous chromosomal abnormalities. Alterations in the TP53 and RB1 tumor suppressor genes are among the most frequently reported genetic events and contribute to uncontrolled cell proliferation, impaired DNA repair, and tumor progression. In a subset of cases, amplification of MDM2 further promotes tumor development by suppressing p53-mediated cellular responses. These molecular abnormalities are closely associated with the aggressive nature of osteosarcoma and its variable response to therapy.(15)

b. Ewing Sarcoma

Ewing sarcoma is a highly aggressive bone and soft tissue malignancy that primarily occurs in children and adolescents. Its defining molecular feature is the EWSR1–FLI1 fusion gene, which results from a reciprocal chromosomal translocation between chromosomes 11 and 22. The resulting fusion protein functions as an abnormal transcription factor that disrupts normal gene regulation, promoting tumor growth and inhibiting cellular differentiation. Because this fusion is highly specific to Ewing sarcoma, it serves as an important diagnostic biomarker. Recent studies also suggest that variations in fusion type and expression may influence disease progression and therapeutic response.(16)

c. Liposarcoma

Liposarcoma is one of the most frequently diagnosed soft tissue sarcomas in adults. Well-differentiated and dedifferentiated liposarcomas are commonly characterized by amplification of the MDM2 gene, often accompanied by CDK4 amplification. Overexpression of MDM2 inhibits the tumor suppressor activity of p53, allowing malignant cells to evade apoptosis and continue proliferating. Identification of MDM2 amplification has become an important molecular tool for differentiating liposarcoma from benign adipocytic tumors. Furthermore, therapies targeting the MDM2 pathway are currently being investigated as potential treatment options for these patients.(17)

d. Synovial Sarcoma

Synovial sarcoma is defined by the presence of the SS18–SSX fusion gene, which arises from a chromosomal translocation involving chromosomes X and 18. This fusion protein alters chromatin remodeling and gene transcription, leading to activation of oncogenic signaling pathways. Because the SS18–SSX fusion is highly specific for synovial sarcoma, it is widely used as a reliable molecular marker for diagnosis. Emerging evidence indicates that different fusion variants, such as SS18–SSX1 and SS18–SSX2, may be associated with

differences in tumor behavior and patient prognosis.(18, 19)

Clinical Significance of Molecular Alterations

The identification of molecular alterations has significantly improved the diagnosis and management of sarcomas. While conventional diagnosis has traditionally relied on histopathological examination, many sarcoma subtypes share similar microscopic features, making accurate classification difficult. The incorporation of molecular biomarkers, including EWSR1–FLI1, SS18–SSX, and MDM2 amplification, has enhanced diagnostic precision and reduced uncertainty, particularly in challenging cases.(20, 21)

Beyond diagnosis, these genetic alterations provide valuable prognostic information. Mutations involving TP53, RB1, and MDM2 are frequently associated with aggressive tumor behavior, increased metastatic potential, and poorer clinical outcomes. Likewise, specific fusion gene variants may influence disease progression and help predict patient prognosis.

The growing understanding of sarcoma genomics has also accelerated the development of targeted therapeutic strategies. Agents directed against the MDM2 pathway are currently undergoing clinical evaluation for MDM2-amplified liposarcomas, while novel therapies targeting the EWSR1–FLI1 fusion and its downstream signaling pathways are being actively investigated for Ewing sarcoma. In synovial sarcoma, the recognition of epigenetic changes induced by the SS18–SSX fusion has stimulated interest in chromatin-modifying therapies as a potential treatment approach.

Overall, integrating molecular profiling into routine clinical practice has strengthened precision oncology in sarcoma by improving diagnostic accuracy, refining risk stratification, identifying therapeutic targets, and enabling more individualized treatment strategies (Figure 4).(22)

RADIOGENOMIC APPLICATIONS IN SARCOMA

Diagnostic Applications

Radiogenomics has emerged as a promising tool for improving the diagnosis and classification of sarcomas by combining quantitative imaging features with molecular information. Conventional diagnosis primarily depends on histopathological evaluation of biopsy specimens; however, tissue sampling may not fully capture the biological complexity of these highly heterogeneous tumors. Radiogenomic approaches overcome this limitation by analyzing imaging characteristics from routine modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) to predict underlying molecular alterations.

Quantitative imaging features, including tumor morphology, margin characteristics, texture, signal intensity, and contrast enhancement patterns, have been shown to reflect important biological properties of sarcomas. Several studies have reported associations between MRI-derived texture features and MDM2 amplification in liposarcoma, as well as TP53 alterations in osteosarcoma, suggesting that radiogenomics can assist in distinguishing tumor subtypes before invasive diagnostic procedures. In addition, imaging biomarkers related to tumor vascularity, necrosis, and intratumoral heterogeneity have been linked to high-grade and biologically aggressive sarcomas. Consequently, radiogenomics has the potential to complement conventional imaging by improving diagnostic accuracy, guiding biopsy toward the most representative tumor regions, and facilitating early identification of aggressive disease.(23, 24)

Prognostic Assessment and Predictive Modeling

In addition to diagnosis, radiogenomics provides valuable prognostic information by enabling non-invasive assessment of tumor behavior and clinical outcomes. Quantitative imaging biomarkers have been associated with important prognostic indicators, including overall survival, disease recurrence, metastatic risk, and response to treatment in both bone and soft tissue sarcomas.

Recent investigations have demonstrated that increased intratumoral heterogeneity, measured through radiomic texture analysis, is associated with more aggressive tumor biology and poorer clinical outcomes. For example, MRI-derived radiomic features have been linked to early local recurrence and distant metastasis in patients with soft tissue sarcoma, whereas CT-based radiomic heterogeneity has been associated with reduced event-free survival and increased chemoresistance in osteosarcoma. These findings have encouraged the development of radiogenomic prediction models that integrate imaging, molecular, and clinical data to estimate individual patient risk. Such models may support personalized treatment planning by improving prognostic stratification, optimizing surveillance strategies, and assisting clinicians in selecting the most appropriate therapeutic approach.

Treatment Planning and Therapeutic Monitoring

Radiogenomics is increasingly being explored as a tool for treatment selection and monitoring therapeutic response. By correlating imaging biomarkers with genomic profiles, clinicians can better predict the likelihood of response to chemotherapy, radiotherapy, and targeted therapies before treatment is initiated.

During therapy, radiogenomic analysis allows continuous evaluation of tumor biology by detecting subtle imaging changes that may precede measurable changes in tumor size. This enables earlier identification of treatment response or emerging therapeutic resistance compared with conventional response assessment methods. Furthermore, artificial intelligence (AI) and machine learning (ML) algorithms that combine radiomic features with gene expression data have demonstrated encouraging performance in distinguishing responders from non-responders. These advances support adaptive treatment strategies in which therapeutic decisions can be modified according to the evolving biological characteristics of the tumor, ultimately improving individualized patient care.

Radiogenomics in Pediatric and Adult Sarcomas

Radiogenomic characteristics differ between pediatric and adult sarcomas because of their distinct biological and molecular profiles. Pediatric sarcomas, including osteosarcoma and Ewing sarcoma, are frequently driven by specific chromosomal translocations or single-driver genetic alterations. In contrast, adult sarcomas generally exhibit more complex genomic landscapes with multiple accumulated genetic abnormalities.

These biological differences are also reflected in imaging characteristics. Pediatric sarcomas often demonstrate relatively homogeneous imaging appearances and well-defined tumor margins, whereas adult sarcomas typically display greater structural and textural heterogeneity, consistent with their more complex molecular composition. Emerging radiogenomic studies have identified imaging biomarkers associated with molecular alterations specific to pediatric sarcomas, such as radiomic features correlated with EWSR1–FLI1 fusion status in Ewing sarcoma. Recognizing these age-related differences is essential for developing robust radiogenomic models that accurately reflect the underlying biology of different patient populations. Such age-specific approaches may enhance diagnostic precision, improve prognostic assessment, and facilitate personalized treatment strategies for both pediatric and adult patients with sarcoma.

CURRENT CLINICAL EVIDENCE

Summary of Key Clinical Studies

Radiogenomics in sarcoma is an evolving field that has gained considerable attention over the past decade. Although clinical evidence is still limited, an increasing number of studies have demonstrated the potential of combining quantitative imaging with molecular information to improve patient management. Most published investigations are retrospective and have been conducted at single institutions, with relatively few multicenter studies available. Magnetic resonance imaging (MRI) remains the most widely used imaging modality, followed by computed tomography (CT), owing to their ability to provide detailed structural and functional information.

Current research has primarily focused on developing radiomic models to predict clinically relevant outcomes, including tumor grade, response to neoadjuvant chemotherapy, local recurrence, metastatic potential, and overall survival. More recently, multicenter studies and systematic reviews have reported improved model performance and broader applicability across different patient populations. However, studies that comprehensively integrate imaging features with genomic, transcriptomic, or other multi-omics data remain relatively uncommon, highlighting an important area for future research.

Performance of Radiogenomic Models

The diagnostic and prognostic performance of radiogenomic models varies according to tumor subtype, imaging modality, feature extraction methods, and validation strategy. In osteosarcoma, MRI-based radiomic models have demonstrated promising results for predicting response to neoadjuvant chemotherapy, with reported area under the receiver operating characteristic curve (AUC) values generally ranging from 0.70 to 0.88. Some multicenter models that combine diffusion-weighted MRI with clinical variables have achieved AUC values approaching 0.85, together with satisfactory sensitivity and specificity.

Similarly, radiomic models developed for survival prediction and risk stratification have shown concordance indices ranging from approximately 0.74 to 0.81, indicating moderate to good predictive performance. Systematic reviews have reported median AUC values between 0.82 and 0.91 across various diagnostic and prognostic applications. Despite these encouraging findings, model performance often declines during external validation, suggesting that many algorithms are affected by overfitting and may not generalize well across different clinical settings.(25, 26)

Limitations of Current Evidence

Despite the encouraging progress, several challenges continue to limit the routine clinical implementation of radiogenomics in sarcoma.

A major limitation is the relatively small sample size of most published studies. Because sarcomas are rare malignancies, many investigations include only a limited number of patients, reducing statistical power and increasing the risk of model overfitting. Furthermore, the predominance of retrospective study designs introduces potential selection bias and limits the strength of clinical evidence.

Another important challenge is the lack of external validation. Most predictive models have been developed and evaluated using data from a single institution, with relatively few undergoing independent validation in multicenter cohorts. Without external validation, it is difficult to determine whether these models will perform reliably in different patient populations or imaging environments.

Variability in imaging acquisition protocols also remains a significant concern. Differences in scanner manufacturers, acquisition parameters, reconstruction algorithms, and tumor segmentation techniques can substantially influence radiomic feature extraction, reducing reproducibility across institutions. Greater standardization of imaging protocols and feature extraction methods is therefore essential.

In addition, although the field is commonly referred to as *radiogenomics*, many published studies rely primarily on radiomic features with limited incorporation of genomic or other multi-omics data. Comprehensive integration of imaging, genomic, transcriptomic, and proteomic information remains relatively rare, restricting the ability to fully characterize the biological mechanisms underlying imaging phenotypes.

Finally, the clinical translation of radiogenomic models is hindered by limited interpretability and insufficient prospective validation. Many machine learning and deep learning algorithms function as "black-box" models, making their predictions difficult to explain and reducing clinician confidence. Large prospective multicenter studies, standardized reporting guidelines, and regulatory validation are still needed before radiogenomics can be routinely incorporated into clinical decision-making for patients with sarcoma.

CHALLENGES AND LIMITATIONS

Although radiogenomics has demonstrated considerable potential for improving the diagnosis and management of sarcomas, several technical, biological, and clinical challenges continue to limit its routine implementation. Addressing these limitations is essential for translating radiogenomic research into everyday clinical practice.

Variability in Imaging Acquisition

A major obstacle to radiogenomic research is the lack of consistency in imaging protocols across healthcare institutions. Variations in scanner manufactur-

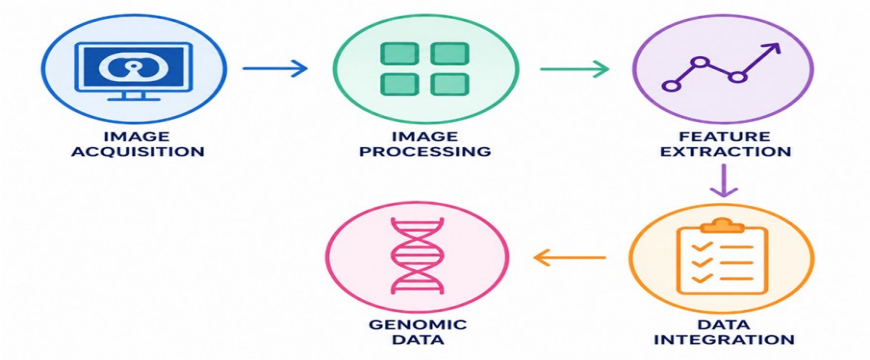

Figure 3: Workflow of Radiogenomics Analysis

ers, magnetic field strength, image acquisition parameters, slice thickness, contrast administration, and reconstruction techniques can substantially influence image quality and the quantitative features extracted from medical images. Even minor differences in patient positioning or scanning conditions may affect radiomic measurements, reducing the reproducibility of study findings. Although initiatives such as the Image Biomarker Standardisation Initiative (IBSI) have proposed standardized guidelines for radiomic analysis, consistent implementation across clinical centers remains limited.

Lack of Standardization in Radiomic Feature Extraction

Reliable radiogenomic analysis depends on standardized methods for image processing and feature extraction. However, considerable variability exists in tumor segmentation techniques, image preprocessing procedures, and feature calculation algorithms. Manual segmentation is time-consuming and subject to observer variability, whereas automated methods may struggle to accurately delineate tumors with irregular margins, necrosis, or heterogeneous internal architecture, which are common characteristics of sarcomas. Furthermore, differences in image normalization, resampling, filtering, and feature definitions often produce inconsistent results between studies. Although software platforms such as PyRadiomics and standardized reporting recommendations have improved reproducibility, universally accepted analytical pipelines have not yet been established.

Integration of Multi-Omics Data

One of the primary goals of radiogenomics is to combine imaging biomarkers with genomic, transcriptomic, proteomic, and other molecular datasets to provide a comprehensive understanding of tumor biology. However, integrating these diverse data types presents substantial computational challenges. Omics datasets are typically high-dimensional, heterogeneous, and generated using different analytical platforms, requiring sophisticated preprocessing, feature selection, and machine learning techniques to identify meaningful biological relationships. In sarcoma, the rarity of the disease further complicates this process, as obtaining matched imaging and molecular data from sufficiently large patient cohorts remains difficult.

Limited Availability of Large Multicenter Datasets

Most published radiogenomic studies in sarcoma have been conducted using relatively small, retrospective cohorts from single institutions. Limited sample sizes reduce statistical power, increase the likelihood of overfitting, and restrict the generalizability of predictive models. External validation using independent patient populations is therefore often lacking. Establishing large, multicenter collaborations and standardized data-sharing initiatives will be essential for overcoming these limitations. Public repositories such as The Cancer Imaging Archive (TCIA) and the Genomic Data Commons (GDC) provide valuable resources for integrating imaging and molecular data, but sarcoma-specific datasets remain limited. Expanding these collaborative databases will be crucial for developing robust, reproducible, and clinically applicable radiogenomic models.(23)(2)(27)(28)

FUTURE PERSPECTIVES

Artificial Intelligence and Deep Learning in Radiogenomics

Artificial intelligence (AI), particularly deep learning, is expected to play a pivotal role in the future development of radiogenomics. Conventional radiomic approaches rely on manually engineered imaging features, whereas deep learning algorithms can automatically learn complex patterns directly from medical images. This capability enables the identification of subtle imaging characteristics that may reflect underlying molecular and genetic alterations. By integrating imaging and genomic data, AI-driven models have the potential to improve diagnostic accuracy, predict treatment response, and facilitate personalized clinical decision-making. In addition, the development of explainable AI methods is helping to improve the transparency and interpretability of predictive models, thereby increasing clinician confidence and supporting their integration into routine clinical practice.

Integration with Multi-Omics Approaches

Radiogenomics is increasingly expanding beyond the integration of imaging and genomics to include other molecular disciplines such as transcriptomics, proteomics, and metabolomics. While genomic analysis identifies genetic alterations, proteomic and metabolomic profiling provide insights into protein expression, cellular signaling, and metabolic activity, offering a more comprehensive understanding of tumor biology. Combining these complementary datasets with quantitative imaging features can improve the identification of biomarkers associated with tumor progression, therapeutic response, and drug resistance. Advances in computational biology and multimodal machine learning are making multi-omics integration more practical and are expected to enhance the predictive performance of future radiogenomic models.

Guiding Targeted and Immunotherapies

Radiogenomics has the potential to support precision oncology by identifying patients who are most likely to benefit from targeted therapies and immunotherapy. Imaging biomarkers associated with specific genetic alterations, tumor mutational burden, or characteristics of the tumor immune microenvironment may provide non-invasive indicators of treatment sensitivity. In addition to patient selection, radiogenomic analysis may enable continuous monitoring of treatment response and facilitate the early detection of therapeutic resistance. Although encouraging results have been reported in several cancer types, further validation is required before these approaches can be routinely applied to different sarcoma subtypes.

Clinical Translation and Decision Support Systems

The successful clinical implementation of radiogenomics will depend on prospective validation through large, multicenter clinical trials. Incorporating radiogenomic biomarkers into clinical trial design may improve patient stratification, support individualized treatment selection, and accelerate the evaluation of novel therapeutic strategies. Emerging technologies such as federated learning offer additional opportunities by enabling collaborative model development across multiple institutions while maintaining patient privacy and data

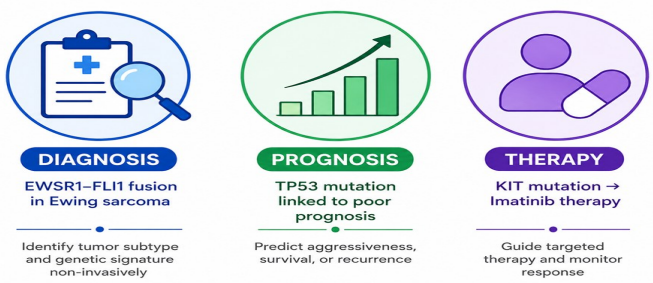

Figure 4: Relevance of Radiogenomics Markers

security. Furthermore, integrating radiogenomic models into clinical decision support systems and electronic health records could provide clinicians with real-time, evidence-based recommendations for diagnosis, prognosis, and treatment planning. Continued efforts toward data standardization, regulatory approval, and ethical governance will be essential to ensure the safe and effective adoption of these technologies in routine sarcoma care.

CONCLUSION

Radiogenomics represents a significant advancement in precision oncology by integrating quantitative imaging biomarkers with genomic and molecular information to provide a more comprehensive understanding of sarcoma biology. This emerging approach offers a non-invasive means of characterizing tumor heterogeneity, improving diagnostic accuracy, predicting prognosis, assessing treatment response, and supporting personalized therapeutic decision-making. Recent advances in radiomics, artificial intelligence, and machine learning have further enhanced the ability to identify meaningful associations between imaging phenotypes and molecular alterations, demonstrating the potential of radiogenomics as a valuable clinical tool. However, despite these encouraging developments, several barriers continue to limit its widespread clinical implementation, including the rarity and heterogeneity of sarcomas, small patient cohorts, variability in imaging protocols, lack of standardized radiomic workflows, and insufficient external validation of predictive models. In addition, integrating imaging data with genomic and other multi-omics datasets remains computationally challenging and requires robust analytical frameworks and collaborative research efforts. Future progress will depend on the establishment of standardized imaging protocols, large multicenter datasets, prospective clinical studies, and the continued development of explainable artificial intelligence models that are reliable, reproducible, and clinically interpretable. As these challenges are progressively addressed, radiogenomics is expected to become an integral component of precision medicine, enabling more accurate diagnosis, improved risk stratification, individualized treatment planning, and real-time disease monitoring. Ultimately, the successful integration of radiogenomics into routine clinical practice has the potential to improve patient outcomes while reducing dependence on invasive diagnostic procedures, thereby transforming the management of both bone and soft tissue sarcomas.

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