International Journal of Research in Engineering and Management Sciences (IJREMS)
E-ISSN: 3107-7439

Research Article
VOL.: 2, Issue: 5, May 2026

Digital Twin Architectures for Personalized Cancer Imaging, Disease Progression Modeling, and Precision Oncology

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ABSTRACT:
Digital twin technology is emerging as a transformative paradigm in precision oncology by enabling the creation of dynamic, patient-specific virtual representations that continuously integrate multimodal imaging, molecular profiles, pathological findings, and longitudinal clinical data. Originally developed for the aerospace and manufacturing industries, digital twins have rapidly evolved into a promising healthcare technology capable of simulating disease progression, predicting treatment outcomes, and supporting individualized clinical decision-making. In oncology, digital twin frameworks combine advanced medical imaging, radiomics, artificial intelligence (AI), machine learning, computational modeling, and mechanistic biological simulations to generate comprehensive virtual models that accurately reflect tumor behavior and patient-specific disease evolution.

Recent advances have expanded the application of digital twins across the cancer care continuum, including tumor detection and segmentation, disease progression modeling, treatment response prediction, radiotherapy planning, surgical guidance, immunotherapy optimization, and longitudinal monitoring of therapeutic outcomes. The integration of multimodal imaging with genomics, pathology, and electronic health records is further enhancing the accuracy and clinical utility of these predictive models, enabling increasingly personalized approaches to cancer management. Emerging technologies such as deep learning, foundation models, federated learning, and multi-omics integration are expected to further accelerate the development of clinically deployable digital twin ecosystems.

Despite their considerable promise, several challenges continue to limit widespread clinical implementation, including limited data interoperability, lack of standardized data acquisition and validation protocols, concerns regarding model interpretability and reproducibility, computational complexity, regulatory uncertainty, and ethical issues related to privacy and data governance. Addressing these challenges will be essential for translating digital twin technologies from research environments into routine clinical practice.

This review provides a comprehensive overview of digital twin architectures for personalized cancer imaging and disease progression modeling, summarizes current applications across major malignancies, discusses enabling technologies and methodological frameworks, critically evaluates existing limitations, and highlights future directions toward intelligent, continuously learning digital twin ecosystems for precision oncology. The convergence of digital twins, artificial intelligence, multimodal imaging, and computational oncology has the potential to fundamentally transform personalized cancer diagnosis, therapeutic planning, response assessment, and long-term disease management.

Keywords: Digital twins; Precision oncology; Medical imaging; Artificial intelligence; Machine learning; Radiomics; Disease progression modeling; Personalized medicine; Computational oncology; Treatment response prediction.

Received Date: 7 May 2026**; Accepted Date:** 17 May 2026**; Published Date:** 24 May 2026.

1. Introduction

The emergence of digital twin technology represents a paradigm shift in precision oncology, offering unprecedented opportunities to transform cancer diagnosis, treatment planning, response assessment, and longitudinal disease monitoring. Cancer remains one of the leading causes of morbidity and mortality

worldwide, with marked interpatient and intratumoral heterogeneity contributing to highly variable therapeutic responses and clinical outcomes [1]. Conventional oncology largely relies on static imaging assessments, tissue biopsies, and population-based clinical guidelines, approaches that often fail to capture the dynamic and evolving biological complexity of individual tumors. Consequently, there is an increasing need for computational frameworks capable of continuously integrating patient-specific data to support personalized clinical decision-making.

A cancer digital twin is a dynamic, patient-specific virtual representation that continuously incorporates multimodal information—including genomic, transcriptomic, proteomic, radiologic, pathologic, clinical, and real-time physiological data—to model disease evolution, predict therapeutic response, and simulate individualized treatment strategies [1]. Unlike conventional predictive models that provide static risk estimates, digital twins evolve throughout the patient's clinical journey by assimilating newly acquired data, thereby enabling continuous refinement of disease modeling and therapeutic recommendations. This adaptive learning capability represents a major advance toward truly individualized precision oncology [1].

Although digital twins originated in the aerospace, automotive, and manufacturing industries, advances in biomedical data acquisition, computational biology, mathematical modeling, and artificial intelligence have accelerated their translation into healthcare. Improvements in high-throughput sequencing, quantitative pathology, multimodal medical imaging, wearable biosensors, electronic health records, and cloud computing have created an unprecedented opportunity to construct comprehensive computational models that accurately represent patient-specific tumor biology [2–4]. Recognizing this potential, the United States National Cancer Institute and the United States Department of Energy launched collaborative initiatives in 2020 to advance the development of predictive Cancer Patient Digital Twins through interdisciplinary research integrating oncology, computational science, and advanced computing technologies [5].

Medical imaging constitutes one of the foundational components of digital twin ecosystems. Imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound, and hybrid imaging techniques provide detailed, non-invasive characterization of tumor morphology, vascularity, metabolism, and functional biology across the entire disease course [6]. These imaging datasets, when integrated with radiomics, radiogenomics, pathology, and molecular profiling, provide comprehensive quantitative information that supports patient-specific disease modeling and virtual simulation of tumor behavior. Recent advances in artificial intelligence and machine learning have further enhanced these capabilities through automated image segmentation, quantitative feature extraction, predictive analytics, and longitudinal modeling, enabling increasingly accurate prediction of disease progression and treatment outcomes [7].

Beyond imaging, digital twin frameworks integrate diverse clinical and biological information—including genomics, proteomics, metabolomics, immune profiling, environmental factors, sociodemographic characteristics, and real-world patient data—to generate continuously evolving computational representations of health and disease [8,9]. These integrated models have the potential to simulate multiple therapeutic scenarios, optimize treatment selection, anticipate disease progression, evaluate toxicity risks, and support adaptive clinical decision-making throughout the cancer care continuum.

This review provides a comprehensive overview of digital twin architectures for personalized cancer imaging and disease progression modeling, with a particular focus on advances reported between 2020 and 2026. We discuss the fundamental principles underlying digital twin technology, enabling computational and imaging methodologies, current clinical applications across major cancer types, and emerging innovations involving radiomics, deep learning, foundation models, federated learning, and multi-omics integration. Finally, we critically evaluate current challenges—including data interoperability, model validation, interpretability, regulatory considerations, and clinical implementation—and outline future directions for realizing intelligent, continuously learning digital twin ecosystems that support next-generation precision oncology.

2. Concept and Architecture of Digital Twins in Oncology

A digital twin is a dynamic virtual representation of a physical object, biological system, or individual that continuously evolves by integrating real-time and longitudinal data. Unlike conventional computational models that provide static predictions, digital twins are designed to mirror the current state of their physical counterparts, enabling continuous simulation, prediction, and optimization of future behavior [10]. In healthcare, digital twin technology extends beyond virtual representations of medical devices to encompass patient-specific computational models that integrate multimodal biomedical data for personalized clinical decision-making. Rather than operating directly on raw patient information, digital twins transform imaging, molecular, physiological, and clinical data into an interactive computational framework that allows clinicians to perform virtual therapeutic simulations before implementing interventions in real patients [11].

In oncology, digital twins represent comprehensive computational ecosystems capable of modeling tumor initiation, progression, treatment response, and long-term disease evolution. These virtual patient models integrate diverse sources of biological and clinical information to simulate multiple therapeutic scenarios, optimize treatment strategies, and support precision medicine. The architecture of a cancer digital twin consists of multiple interconnected computational layers that continuously exchange information, allowing the model to evolve as new patient data become available [12].

2.1 Patient Data Acquisition and Integration Layer

The foundation of every cancer digital twin is the acquisition and harmonization of heterogeneous patient data collected throughout the clinical journey. This layer integrates electronic health records, demographic characteristics, laboratory investigations, treatment history, pathological findings, genomic and transcriptomic profiles, proteomic and metabolomic datasets, medical imaging studies, and physiological information obtained from wearable sensors and remote monitoring devices [13]. Standardized data integration ensures that the virtual patient accurately reflects both the biological characteristics of the tumor and the overall health status of the individual.

2.2 Medical Imaging and Radiomics Layer

Medical imaging serves as one of the primary data sources for digital twin construction because it provides comprehensive, non-invasive characterization of tumor anatomy, physiology, metabolism, and temporal evolution. Imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound, and hybrid imaging contribute complementary information describing tumor morphology and biological behavior.

Radiomics further expands the value of medical imaging by extracting hundreds to thousands of quantitative features describing tumor shape, intensity, texture, spatial organization, and higher-order imaging characteristics. These quantitative biomarkers capture intratumoral heterogeneity and imaging phenotypes that are often imperceptible during routine visual interpretation. Longitudinal radiomic analysis enables continuous monitoring of disease progression and treatment response, making imaging an indispensable component of patient-specific digital twin ecosystems [14].

2.3 Artificial Intelligence and Machine Learning Layer

Artificial intelligence and machine learning constitute the analytical engine of digital twin systems. These computational approaches identify complex, nonlinear relationships among imaging, molecular, pathological, and clinical variables that cannot be recognized using conventional statistical methods. Machine learning algorithms support predictive modeling, patient stratification, survival estimation, toxicity prediction, and treatment response assessment, while deep learning automatically learns hierarchical feature representations directly from high-dimensional imaging data. Together, these approaches enable increasingly accurate prediction of disease trajectories and individualized therapeutic outcomes [15].

2.4 Biological and Mechanistic Modeling Layer

Although data-driven artificial intelligence provides highly accurate predictive capabilities, mechanistic biological modeling offers complementary insights

by explicitly representing the biological processes underlying tumor growth and therapeutic response. Mathematical and computational models simulate cancer cell proliferation, angiogenesis, immune interactions, metastatic dissemination, pharmacokinetics, pharmacodynamics, and radiation response across multiple biological scales. Integrating mechanistic models with artificial intelligence improves biological interpretability while enabling virtual testing of alternative therapeutic strategies before clinical implementation [16,17].

2.5 Simulation and Predictive Analytics Layer

The defining feature of digital twin technology is its ability to perform patient-specific virtual simulations. By continuously integrating updated clinical information, digital twins can model tumor evolution, estimate disease progression, predict therapeutic efficacy, evaluate treatment-related toxicity, and compare multiple intervention strategies within a risk-free computational environment. Such predictive simulations have demonstrated promising applications in radiotherapy planning, systemic therapy optimization, immunotherapy response prediction, adaptive treatment strategies, stereotactic radiotherapy, FLASH radiotherapy, immune-radiotherapy, and longitudinal disease monitoring [17,18].

2.6 Clinical Decision Support Layer

Outputs generated by digital twin simulations are translated into clinically actionable information through integrated decision-support systems. These platforms combine multimodal imaging, molecular profiling, pathology, laboratory investigations, and real-world patient data to assist clinicians in selecting personalized therapies, optimizing treatment timing, anticipating adverse events, and monitoring disease progression. Artificial intelligence–driven decision-support systems continuously update recommendations as new clinical information becomes available, enabling adaptive and evidence-based precision oncology throughout the patient's treatment journey [11,19].

2.7 Dynamic Feedback and Continuous Learning

A distinguishing characteristic of cancer digital twins is their ability to continuously evolve through dynamic feedback loops between the virtual model and the physical patient. As new imaging studies, laboratory results, molecular analyses, and treatment outcomes become available, these data are incorporated into the computational framework, allowing the digital twin to refine predictions and improve simulation accuracy over time. This continuous learning capability transforms digital twins from static predictive models into adaptive, intelligent clinical systems capable of supporting real-time precision medicine and individualized cancer management [20].

3. Role of Medical Imaging in Cancer Digital Twins

Medical imaging provides the visual and quantitative foundation for digital twin development in precision oncology by enabling comprehensive characterization of tumor anatomy, physiology, metabolism, and longitudinal disease evolution. As a non-invasive technology, medical imaging supports continuous monitoring throughout the cancer care continuum, facilitating individualized diagnosis, treatment planning, response assessment, and surveillance. By integrating imaging-derived information with molecular, pathological, and clinical data, digital twin systems generate patient-specific computational models capable of simulating disease progression and optimizing therapeutic strategies [6].

3.1 Multimodal Imaging Integration

The accuracy and clinical utility of cancer digital twins depend heavily on the integration of complementary imaging modalities, each providing unique information regarding tumor biology. Computed tomography (CT) offers high-resolution anatomical visualization, magnetic resonance imaging (MRI) provides superior soft-tissue contrast and functional characterization, positron emission tomography (PET) evaluates metabolic activity, while ultrasound contributes real-time structural and vascular assessment. The integration of these modalities enables comprehensive representation of tumor morphology, heterogeneity, vascularity, metabolism, and surrounding tissue characteristics.

Recent advances in multimodal imaging integration and machine learning have substantially improved digital twin fidelity despite ongoing challenges related to anatomical complexity, multimodal data fusion, and computational requirements [6]. For example, deep learning models integrating contrast-enhanced T1-weighted (T1CE) and Fluid-Attenuated Inversion Recovery (FLAIR) MRI

sequences have demonstrated excellent segmentation performance, achieving Dice coefficients of 84.81% for peritumoral edema, 76.99% for enhancing tumor regions, and 72.25% for necrotic tissue, illustrating the value of multimodal image fusion for accurate tumor characterization [21].

3.2 Automated Tumor Segmentation

Accurate tumor segmentation is a fundamental step in digital twin construction because it defines the anatomical boundaries from which quantitative imaging features and computational simulations are derived. Manual segmentation is labor-intensive, time-consuming, and susceptible to interobserver variability, making automated segmentation an essential component of scalable digital twin platforms.

Recent developments in artificial intelligence, particularly deep learning, have significantly improved automated medical image segmentation across multiple imaging modalities and disease types. Foundation models have further advanced this field by providing generalized segmentation capabilities that extend beyond individual cancer types. MedSAM, one of the largest medical image foundation models, was trained using more than 1.57 million image-mask pairs spanning ten imaging modalities and over thirty cancer types, demonstrating the potential for universal medical image segmentation within digital twin ecosystems [22]. In radiation oncology, automated segmentation combined with mathematical tumor growth models enables more accurate target delineation, adaptive radiotherapy planning, and personalized treatment optimization throughout the patient journey [23].

3.3 Radiomics and Quantitative Imaging Biomarkers

Radiomics has become one of the most important computational components of digital twin technology by converting routine medical images into high-dimensional quantitative data. Hundreds to thousands of imaging biomarkers describing tumor shape, intensity, texture, wavelet characteristics, and spatial heterogeneity can be extracted from CT, MRI, PET, and ultrasound images. These quantitative features provide objective measurements of tumor phenotype that often reflect underlying biological processes not visible during conventional image interpretation [14].

The integration of radiomics with machine learning enables discovery of complex imaging signatures associated with tumor aggressiveness, molecular alterations, therapeutic response, and patient prognosis. These quantitative imaging biomarkers significantly enhance patient stratification and support personalized therapeutic decision-making, thereby strengthening the predictive capabilities of cancer digital twins [24].

3.4 Artificial Intelligence for Image Analysis and Outcome Prediction

Artificial intelligence has transformed medical image analysis by enabling automated detection, segmentation, feature extraction, disease classification, prognostic modeling, and treatment response prediction. Deep learning architectures are capable of learning complex hierarchical imaging representations directly from raw medical images without requiring manual feature engineering, resulting in improved predictive performance across numerous oncology applications.

Recent studies have demonstrated the ability of deep learning models to accurately predict treatment response using multiparametric imaging. For example, Liu and colleagues developed a deep learning radiomics signature (DLRS) based on multiparametric MRI for predicting distant metastasis in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy. The proposed model achieved a three-year area under the receiver operating characteristic curve (AUC) of 0.894 in the validation cohort, illustrating the potential of artificial intelligence–driven imaging biomarkers for personalized prognosis and therapeutic decision-making [15].

Collectively, advances in multimodal imaging, automated segmentation, radiomics, and artificial intelligence have substantially strengthened the development of patient-specific digital twins. By integrating high-dimensional imaging information with molecular, pathological, and clinical datasets, these technologies enable increasingly accurate simulation of tumor behavior, prediction of disease progression, and optimization of individualized cancer treatment strategies.

4. Artificial Intelligence and Machine Learning Integration

Advanced machine learning and deep learning architectures form the computational foundation enabling digital twins to identify complex patterns within high-dimensional, multimodal data and generate personalized predictions.

Deep Learning Architectures for Medical Imaging: This comprehensive review explores the role of deep learning (DL) in glioma segmentation using multiparametric magnetic resonance imaging (MRI) data. The study surveys advanced techniques such as multiparametric MRI for capturing the complex nature of gliomas. It delves into the integration of DL with MRI, focusing on convolutional neural networks (CNNs) and their remarkable capabilities in tumor segmentation. [25] We propose a novel cross-modal attention fusion-based deep neural network (CMAF-Net) for incomplete multimodal brain tumor segmentation, which is based on a three-dimensional (3D) U-Net architecture with encoding and decoding structure, a 3D Swin block, and a cross-modal attention fusion (CMAF) block. [26]

A 2.5D hybrid convolutional neural network was proposed to simultaneously localize glioma and classify its molecular status by leveraging MRI imaging features and prior knowledge features from clinical records and tumor location. [27] A brain tumor is an uncontrolled growth of cancerous cells in the brain. Accurate segmentation and classification of tumors are critical for subsequent prognosis and treatment planning. This work proposes context aware deep learning for brain tumor segmentation, subtype classification, and overall survival prediction using structural multimodal magnetic resonance images (mMRI). [28]

Multimodal Data Integration: By analyzing multi-dimensional, multiomic, spatial pathology, and radiomic data, these technologies enable a deeper understanding of the intricate molecular pathways, aiding in the identification of critical nodes within the tumor's biology to optimize treatment selection. [7] Digitized histopathological tissue slides and genomics profiling data are available for many patients with solid tumors. In the last 5 years, Deep Learning (DL) has been broadly used to extract clinically actionable information and biological knowledge from pathology slides and genomic data in cancer. In addition, a number of recent studies have introduced multimodal DL models designed to simultaneously process both images from pathology slides and genomic data as inputs. [29]

Explainable AI and Clinical Interpretability: Model transparency and explainability, achieved through techniques such as Grad-CAM (which generates visual heat maps highlighting regions that influence the model's decision), SHAP (a game-theoretic approach to quantify feature importance), and attention maps (from transformer models), are crucial for building clinician confidence and verifying that model decisions are based on clinically relevant imaging features. [15] Grad-CAM effectively identified regions that were significant for different tumour types, while SHAP analysis provided insights into the importance of individual features. Together, these approaches confirmed the reliability and interpretability of the model, overcoming key challenges in AI-driven medical diagnostics. [30]

Survival Prediction and Prognosis Modeling: Jiang et al. developed and validated a deep learning model utilizing a vision transformer (ViT) architecture to predict overall survival and disease-free survival in patients with rectal cancer using preoperative T2WI. The study included 893 patients from China and Germany, divided into training, validation, internal testing, and external testing cohorts. The model, trained on preoperative T2WI images, achieved a C-index of 0.82 for overall survival prediction in the validation set. [15]

4. Digital Twin Applications in Cancer Disease Progression Modeling

The successful implementation of digital twin technologies across multiple malignancies demonstrates their growing versatility and potential to transform precision oncology. By integrating multimodal imaging, molecular profiling, clinical data, and computational modeling, digital twins support individualized diagnosis, prognostic assessment, treatment planning, response prediction, and longitudinal disease monitoring. Although most applications remain in the research phase, accumulating evidence indicates that digital twin frameworks are increasingly capable of supporting clinically meaningful decision-making across diverse cancer types.

4.1 Brain Cancer and Glioblastoma

Glioblastoma (GBM) represents one of the most promising applications of digital twin technology owing to its aggressive biological behavior, profound intratumoral heterogeneity, and limited therapeutic options. Recent computational models

have integrated molecular biomarkers, imaging features, and clinical variables to generate individualized prognostic predictions before treatment initiation.

One notable example is an artificial neural network (ANN) developed using four readily available pre-treatment variables: CUL2 copy number variation, patient age, Karnofsky Performance Scale (KPS), and the surface-to-volume (SvV) ratio. This four-layer deep learning model predicted overall survival with an accuracy of 80–85%, demonstrating that reliable prognostic modeling can be achieved without invasive intracranial biopsy procedures [31].

Advanced multimodal imaging has further strengthened glioblastoma digital twins. The BRIDGE co-registration framework integrates in vivo magnetic resonance imaging (MRI) with two-photon microscopy to correlate imaging characteristics with tumor density and growth dynamics over time, thereby improving patient-specific disease modeling [32]. In parallel, mathematical models incorporating T-cell migration, immune dynamics, and radiotherapy have successfully simulated combined radiation-immunotherapy responses. Using simulated annealing optimization, these models achieved a root mean square error of 287 mm^3 while reproducing the experimentally observed PULSAR effect, suggesting that longer intervals between radiation fractions may improve tumor control during immunotherapy [33].

4.2 Lung Cancer

Lung cancer has emerged as another major application area for digital twin technology because of the availability of large-scale imaging datasets and molecular biomarkers. Recent studies have proposed Smart Digital Twin Ecosystems (SDTEs) that integrate thoracic CT imaging, histopathology, genomic alterations—including EGFR, ALK, and KRAS mutations—and longitudinal clinical information to simulate individualized tumor evolution and treatment response [34].

A representative framework incorporated the RETFound foundation model and was trained using 8,420 annotated CT examinations together with 2,135 histopathological samples obtained from public lung cancer datasets. The resulting digital twin achieved an overall accuracy of 98.16%, sensitivity of 97.92%, specificity of 97.53%, recall of 90.23%, and an F1-score of 0.95, highlighting the potential of foundation models for precision lung cancer management [34].

4.3 Breast Cancer

Breast cancer represents an ideal candidate for digital twin implementation because disease progression is influenced by complex interactions among genetic alterations, hormonal signaling, environmental exposures, and lifestyle factors. Digital twin frameworks integrate genomic, biochemical, imaging, and behavioral information to construct individualized computational models capable of supporting early diagnosis, risk stratification, treatment optimization, and survivorship planning [35].

Recent advances in computational biology, mathematical modeling, and artificial intelligence have significantly expanded the feasibility of patient-specific breast cancer digital twins, enabling virtual treatment simulations while promoting personalized therapeutic strategies and greater patient engagement throughout the care pathway [35].

4.4 Prostate Cancer

Digital twin technology is increasingly recognized as a promising framework for personalized prostate cancer management. By combining multiparametric MRI, molecular biomarkers, pathology, clinical information, and physiological data, prostate cancer digital twins can simulate disease progression, predict treatment response, and support adaptive therapeutic decision-making [36].

Such patient-specific computational models have the potential to shift prostate cancer management toward predictive, preventive, personalized, and participatory healthcare, thereby improving clinical outcomes while optimizing healthcare resource utilization [36].

4.5 Colorectal Cancer

Digital twin methodologies are also demonstrating considerable promise in colorectal cancer, particularly in predicting response to neoadjuvant chemoradiotherapy and guiding adjuvant treatment decisions. Machine learning-based radiomics models derived from magnetic resonance imaging

have shown encouraging performance in predicting pathological complete response and long-term clinical outcomes.

Joint analysis of pre-treatment and mid-treatment MRI examinations achieved an area under the receiver operating characteristic curve (AUC) of 0.83 for predicting pathological complete response. Furthermore, machine learning radiomics models based on T2-weighted MRI successfully predicted treatment response in locally advanced rectal cancer, while chemotherapy decision-support models reduced unnecessary adjuvant chemotherapy by approximately 65%, illustrating the clinical value of personalized digital twin-guided therapeutic planning [15].

4.6 Mathematical Modeling of Tumor Growth and Treatment Response

Mathematical and mechanistic modeling forms a critical component of digital twin ecosystems by enabling realistic simulation of tumor growth, angiogenesis, radiation response, and therapeutic efficacy. One of the most advanced examples is the AMBER framework, which combines agent-based modeling with continuous spatiotemporal simulations of the tumor microenvironment, including oxygen distribution, angiogenesis, and vascular endothelial growth factor dynamics [37].

AMBER is integrated with the TOPAS Monte Carlo particle transport platform, enabling simultaneous simulation of heterogeneous radiation dose distributions and biological tumor responses. By coupling physical radiation transport with biological processes that influence radiosensitivity, such as tissue oxygenation, this integrated framework provides realistic patient-specific simulations capable of supporting radiotherapy optimization and future digital twin applications in precision oncology [37].

Collectively, these studies demonstrate that digital twin technologies are evolving from conceptual computational models toward clinically relevant decision-support systems. Their ability to integrate multimodal imaging, molecular biology, artificial intelligence, and mechanistic modeling enables increasingly accurate simulation of disease progression, prediction of therapeutic response, and optimization of personalized cancer treatment across multiple malignancies. As validation studies continue and prospective clinical trials expand, digital twins are expected to become a foundational technology for next-generation precision oncology.

5. Personalized Cancer Treatment Using Digital Twins

Digital twins enable fundamentally new approaches to precision oncology by permitting in silico simulation of treatment responses before clinical administration, thereby optimizing therapeutic selection and reducing adverse effects.

Drug Response Prediction and Treatment Selection: In pharmacotherapy, digital twins combine mechanistic pharmacokinetic-pharmacodynamic modeling with artificial intelligence to simulate drug exposure and therapeutic response prior to treatment administration. This capability allows optimization of dosing, prediction of adverse drug reactions, and selection of individualized therapies. [38] Cancer heterogeneity presents a major obstacle to effective drug treatment, emphasizing the need for personalized approaches that can accurately predict drug responses. Advances in high-throughput technologies have driven precision medicine initiatives toward integrating multi-omics data, enabling a more comprehensive understanding of tumor biology. [39]

Patient-Derived Models and In Silico Trials: Computational models have been successful in predicting drug sensitivity in cancer cell line data, creating an opportunity to guide precision medicine. However, translating these models to tumors remains challenging. We propose a new transfer learning workflow that transfers drug sensitivity predicting models from large-scale cancer cell lines to both tumors and patient derived xenografts based on molecular pathways derived from genomic features. [40] We conducted this co-clinical trial with treatment-naive rectal cancer patients and matched patient-derived tumor organoids to determine whether a correlation exists between experimental results obtained after irradiation in patients and organoids. [41] Our machine learning-based prediction model showed excellent performance. In the prediction model for good responders trained using the random forest algorithm, the area under the curve, accuracy, and kappa value were 0.918, 81.5%, and 0.51, respectively. In the prediction model for poor responders, the area under the curve, accuracy, and kappa value were 0.971, 92.1%, and 0.75, respectively. [41]

Radiotherapy Planning and Optimization: We evaluate the mathematical implications and biological effects of 2 models of RT response on dose personalization: (1) cytotoxicity to cancer cells that lead to direct tumor volume reduction (DVR) and (2) radiation responses to the tumor microenvironment that lead to tumor carrying capacity reduction (CCR) and subsequent tumor shrinkage. [42] Since CT scans form an integral part of radiotherapy, a widely used cancer treatment, we propose the use of CT-derived radiomic features to attempt to predict the course of tumor growth curves. [43]

Immunotherapy and Combination Treatment Optimization: Drug resistance is one of the most intractable issues to the targeted therapy for cancer diseases. To explore effective combination therapy schemes, we propose a mathematical model to study the effects of different treatment schemes on the dynamics of cancer cells. [44] Simulation results suggest that immunotherapy combined with chemotherapy contributes significantly to the control of tumor growth compared to monotherapy. [44] We present a novel macroscopic approach designed to quantitatively analyze the intricate dynamics governing the interactions among the immune system, radiotherapy, and tumor progression. Building upon previous research demonstrating the synergistic effects of radiotherapy and immunotherapy in cancer treatment, we provide a comprehensive mathematical framework for understanding the underlying mechanisms driving these interactions. [45]

6. Current Challenges and Limitations

Despite tremendous progress, significant obstacles impede widespread clinical implementation of cancer digital twins, necessitating continued research and infrastructure development.

Data Quality, Standardization, and Interoperability: On the application of data processing and artificial intelligence, the algorithm for combining medical imaging and multi-omics data is the key, and the integration of multi-modal data and dynamic modeling improve the accuracy of the model, but the integration of different data types is limited by the interoperability of the tools and the degree of standardization. [3] Data integration across heterogeneous sources presents substantial technical hurdles, requiring robust frameworks for harmonizing genomic, imaging, and clinical data under findability, accessibility, interoperability, reusability principles. [1]

Model Validation and Clinical Evidence: Importantly, most published work emphasizes technical accuracy, with limited evidence demonstrating that AI-assisted MRI prognostication improves patient outcomes, clinical decision-making, or cost-effectiveness—underscoring a significant translational gap. [15] Several challenges hinder the broader implementation of MDT, including the integration of heterogeneous data sources, interpretability and generalizability of artificial intelligence models, data security and privacy concerns, and the need for scalable computational infrastructures. [46]

Computational Complexity and Infrastructure Requirements: The complexity of cancer biology – including mechanisms of drug resistance, immune responses, and inter-patient heterogeneity – poses challenges for mechanistic modeling, particularly in immuno-oncology, where treatment mechanisms are not fully understood. [1] Widespread implementation faces several challenges: (1) characterizing dynamic molecular changes across multiple biological scales; (2) developing computational methods to integrate data into DTs; (3) prioritizing disease mechanisms and therapeutic targets; (4) creating interoperable DT systems that can learn from each other; (5) designing user-friendly interfaces for patients and clinicians; (6) scaling DT technology globally for equitable healthcare access; (7) addressing ethical, regulatory, and financial considerations. [8]

Regulatory and Ethical Considerations: Regulatory frameworks remain underdeveloped. Bodies, including the Food and Drug Administration and European Medicines Agency will need to establish clear guidelines for validating and deploying digital twins in clinical settings, similar to existing frameworks for medical devices. [1] Furthermore, ethical considerations regarding data privacy, algorithmic bias, and equitable access needs careful attention to ensure this technology benefits all patients. [1]

Clinical Implementation and Workflow Integration: To become a standard of care, these models must demonstrate efficacy and safety through prospective trials, ultimately seeking approval as a software as a medical device (SaMD), a paradigm now being operationalized in pioneering clinical trials. [18] Yet, their routine application in clinical practice remains limited, underscoring a growing

translational gap between digital innovation and healthcare delivery. [47]

7. Future Perspectives

Emerging technological advances and evolving clinical needs point toward a future where digital twins become foundational elements of precision cancer medicine, with several promising directions warranting investigation.

Real-Time Monitoring and Adaptive Treatment: For real-time monitoring and adaptation, digital twins continuously integrate data from clinical encounters, imaging, and even wearable devices to track disease progression and treatment response. This enables clinicians to adjust protocols dynamically – critical in oncology where tumor biology and treatment responsiveness vary significantly over time and between individuals. [1] Predictive analytics and preventive interventions are made possible by machine learning algorithms, allowing for early detection of health risks and proactive interventions. [19]

AI-Powered Autonomous Clinical Decision Systems: In clinical trial design, digital twins enable in silico simulation of trial outcomes, optimizing study designs and accelerating drug development. Virtual patient populations can be generated to test hypotheses, identify potential biomarkers for patient stratification, and predict treatment responses before human exposure – potentially reducing the time and cost associated with traditional clinical trials. [1] Generative AI has the potential to transform the field by leveraging recent developments in deep learning and customizing models for the needs of scientists, physicians and patients. [48]

Multi-Scale and Multi-Organ Modeling: Future research and development opportunities in healthcare span multiple scales, from molecular mechanisms to tissue-scale processes to whole-organism physiology, requiring integration across these biological levels. [4] The massive amount of human biological, imaging, and clinical data produced by multiple and diverse sources necessitates integrative modeling approaches able to summarize all this information into answers to specific clinical questions. [49]

Integration of Genomics and Spatial Omics: Spatial omics technologies correlate molecular signatures within tumor microenvironments, guiding treatment strategies. Bioinformatics integrates these technologies to establish a new standard in precision oncology, thereby enhancing therapy efficacy. [50] Multiomics data integration approaches offer a comprehensive functional understanding of biological systems, with significant applications in disease therapeutics. By providing deep insights into disease-associated molecular mechanisms, multiomics facilitates precision medicine by accounting for individual omics profiles, enabling early disease detection and prevention, aiding biomarker discovery for diagnosis, prognosis, and treatment monitoring, and identifying molecular targets for innovative drug development or the repurposing of existing therapies. [51]

Patient-Centered Design and Equitable Implementation: Future healthcare and public health policy must go beyond technical innovation to address patients' lived experiences, ensuring that digital twins enhance rather than diminish autonomy, trust, and equity. [52] We outline a translational roadmap that emphasizes dynamic model validation, clinician co-development, equitable data representation, and regulatory harmonization. [47]

8. Conclusion

Digital twin technology represents a transformative paradigm shift in oncology, moving cancer care from population-based medicine toward truly individualized, dynamic, predictive therapeutic strategies. Digital twins represent more than incremental technological advancement – they embody a fundamental reconceptualization of cancer care from population-based medicine to truly individualized therapy. [1] In this review, we present the opportunities and challenges of applying digital twins in clinical oncology, with a particular focus on integrating medical imaging with mechanism-based, tissue-scale mathematical modeling. [2]

The successful integration of advanced medical imaging, machine learning algorithms, radiomics analysis, and mechanistic disease progression models has demonstrated the feasibility and clinical utility of digital twins across multiple cancer types, including glioblastoma, lung cancer, breast cancer, prostate cancer, and colorectal cancer. Digital twin technology has obvious advantages in diagnosis, treatment decision-making, prognosis prediction, and surgery planning. [3] AI-generated DTs now offer the potential to accurately diagnose cancer, reveal novel biomarkers, and accelerate drug

development, thus advancing precision medicine. [7]

However, widespread clinical adoption remains limited by challenges in data standardization, model validation, regulatory frameworks, and infrastructure requirements. The effective development and implementation of medical digital twins require a systems-based approach that extends beyond technological advancement to include integrated data infrastructures, interoperability standards, and robust data governance frameworks. Strengthening interdisciplinary collaboration among clinicians, data scientists, engineers, and policymakers is essential for ensuring the safe and effective use of this technology. [46]

Future advancement requires sustained collaborative effort across computational, experimental, and clinical communities. With advancements in AI, wearable technology, and multiomics data integration, DTs are poised to reshape precision medicine. Future research should focus on refining computational efficiency, standardizing data interoperability, and ensuring ethical AI-driven decision-making. [9] The convergence of artificial intelligence, mathematical modeling, and clinical oncology in digital twin technology offers hope for a future where virtual experiments on patient-specific models may guide clinical decisions with unprecedented precision. The convergence of artificial intelligence, mathematical modeling, and clinical oncology in digital twin technology offers hope for a future where virtual experiments on patient-specific models may guide clinical decisions with unprecedented precision. [1] As computational capabilities expand, data integration improves, and validation studies accumulate, digital twins are poised to become foundational elements of next-generation precision oncology, ultimately enabling each cancer patient to receive care optimized specifically for their unique disease biology and individual characteristics.

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