Next-Generation Cancer Treatment Using Digital Twins

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Details:

Publisher: PreferPub (eBook Version) and Kindle (Paperback Version)

Publication Date: October 2026

Language: English

Dimensions: 5 x 0.39 x 8 inches

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ISBN-13: 979-8161130148

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1. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN HEMATOLOGICAL CANCERS

Background

Hematological cancer is a type of malignancy that originates from blood-forming tissues or the lymphatic system. Generally, these cancers are divided into three major types: leukemia, lymphoma, and myeloma. Hematologic neoplasms are relatively common and rank as the fourth most frequently diagnosed group of cancers among both sexes in economically developed regions worldwide, with global prevalence and mortality increasing significantly over the past three decades. Their differences from solid tumors in several aspects present distinct therapeutic challenges, diagnostic protocols, and monitoring approaches. Whereas solid tumors are often treated primarily with surgery, hematologic malignancies are systemic diseases from the outset and circulate as individual malignant cells without forming a discrete physical mass. Accordingly, they are managed mainly with chemotherapy, immunotherapy, and targeted therapy and, where appropriate, radiation therapy and hematopoietic stem cell transplantation. Unlike the surgical management of most solid tumors, chemotherapy remains the first-

line treatment for hematopoietic tumors; however, disease heterogeneity and drug resistance limit its clinical benefit. Most patients initially benefit from apoptosis-inducing chemotherapy, but the majority ultimately experience recurrence, and a minority are inherently resistant to existing therapies. Immunotherapies have shown clinical efficacy in a subset of patients with hematological malignancies. Clinical responses, however, are heterogeneous, including delayed responses, incomplete responses, or primary resistance. Immunotherapy, on the other hand, works through regulation of the body's immune system and therefore results in unique toxicities that have an immunological origin. Allogeneic stem cell transplantation is capable of controlling the condition in some instances for a prolonged period of time; however, there are considerable risks, including graft-versus-host disease (GVHD), infections, and death from the therapy itself. Radiation therapy is another method that can be used under some specific conditions, although its use in disseminated hematologic malignancy is somewhat restricted compared with localized solid tumors. Notwithstanding substantial technological advances that have improved the management of hematologic malignancies, these diseases remain an important cause of morbidity and mortality. Current treatment strategies are primarily guided by population-level clinical trial evidence and es-

tablished prognostic biomarkers. Although valuable, these approaches cannot completely predict individual therapeutic outcomes. A major unmet need exists for technologies capable of integrating diverse biological and clinical information to provide dynamic, patient-specific predictions. This chapter discusses the principles, applications, clinical opportunities, and challenges of digital twin-based precision oncology in hematological malignancies.

Evolution of Precision Oncology in Hematological Malignancies

Current treatment strategies in oncology are primarily guided by population-level clinical trial evidence and established prognostic biomarkers. Although valuable, these approaches cannot completely predict individual therapeutic outcomes. A major unmet need exists for technologies capable of integrating diverse biological and clinical information to provide dynamic, patient-specific predictions. Patients with apparently similar diagnoses may experience substantially different responses to the same therapy due to variations in molecular characteristics, immune function, pharmacokinetics, and disease evolution. Precision oncology has improved treatment selection through genomic classification and biomarker-driven approaches; however, many current strategies provide static representations of a biologically evolving disease. Digital

twin technology introduces a dynamic approach by creating computational models that integrate clinical, molecular, immunological, imaging, and longitudinal treatment-response data to simulate disease behavior and predict therapeutic outcomes. In hematological cancers, digital twins have the potential to improve therapeutic decision-making by supporting individualized treatment selection, predicting response and toxicity, optimizing treatment sequencing, and enabling adaptive disease management.

Definition and Principles of Digital Twins

A digital twin refers to a dynamic computer model of a physical object that integrates continuous data from the real world to model its current state, anticipate future actions, and inform decisions. It was developed in the engineering field for monitoring and optimizing highly complex processes and systems. In healthcare, the digital twin is applied to the modeling of biological systems through data from clinical practice, molecular biology, and physiology. In the oncology field, a digital twin represents a virtual model of a patient's cancer and its dynamics together with the patient's body. While traditional prediction models rely on associations between past events and outcomes, digital twins allow for continuous development by using patient-specific data, including disease dynamics and

treatment responses. In hematologic malignancies, whose behavior is determined by clonal evolution, immune and therapeutic pressures, the digital twin allows for the representation of cancer as a dynamic biological system.

Digital Twin Architecture For Hematological Cancers

A clinically useful digital twin for hematological cancer would require much more than a single artificial intelligence algorithm. It would need to function as an integrated computational environment capable of receiving, organizing, interpreting, and updating information from multiple sources. Medical digital twin frameworks have been described as involving the physical patient, a data connection, a patient-specific computational representation, an interface, and synchronization between the real and virtual states. These components provide a useful conceptual foundation for developing digital twins in hematology.

The physical patient represents the continuously changing biological system. Relevant information could include demographic characteristics, symptoms, physical findings, blood counts, biochemical measurements, bone marrow assessments, pathology reports, imaging results, treatment exposure, adverse events, and clinical outcomes. In hematological cancers, laboratory measurements are particularly important

because blood and bone marrow can provide repeated observations of disease activity. A digital twin could therefore be updated at multiple points during diagnosis, induction therapy, consolidation, maintenance therapy, transplantation, cellular therapy, or relapse management.

The data connection is responsible for bringing new information into the digital twin. This could include laboratory information systems, electronic health records, genomic sequencing platforms, imaging systems, flow cytometry databases, pharmacy records, wearable devices, and patient-reported outcomes. The quality of this connection would strongly influence the reliability of the resulting model. Missing laboratory measurements, inconsistent data formats, delayed sequencing results, or differences between institutions could introduce uncertainty.

The computational patient model would form the core of the digital twin. It could contain several interconnected models rather than one universal algorithm. A mechanistic model might describe leukemia cell growth, treatment effects, or drug pharmacokinetics. A machine learning model might estimate relapse risk or treatment response. A probabilistic model could represent uncertainty when the available evidence is incomplete. Artificial intelligence could also analyze complex imaging, genomic, transcriptomic, or clinical datasets.

Synchronization would allow the digital twin to

evolve alongside the patient. When a new bone marrow assessment indicates a substantial reduction in malignant cells, for example, the computational representation could be updated. If a new mutation is detected, the estimated probability of response to selected therapies could change. If a patient develops severe toxicity, the model could incorporate that information into subsequent treatment simulations.

The interface is equally important. Clinicians cannot effectively use a digital twin if its output is presented as an unexplained numerical score. The system should provide understandable summaries of the patient's current disease state, major predictive factors, treatment alternatives, expected benefits, possible toxicities, and uncertainty. It should allow physicians to compare scenarios without presenting predictions as guaranteed outcomes.

The strongest digital twins will probably combine mechanistic modeling with artificial intelligence. AI can identify complex statistical relationships within large datasets, while mechanistic models can represent biological processes and constraints. Recent work in medical digital twins emphasizes the potential of combining multimodal data, artificial intelligence, and mechanistic modeling rather than relying exclusively on either approach.

Applications In Leukemia,

Lymphoma, And Multiple Myeloma

Digital twins could have distinct applications across different hematological malignancies because each disease presents different biological and clinical challenges. In acute leukemia, treatment decisions often depend on disease genetics, measurable residual disease, response kinetics, patient fitness, and the risk of treatment-related complications. A digital twin could integrate these variables and simulate how malignant cell populations might change during induction or consolidation therapy.

For example, an acute myeloid leukemia digital twin could incorporate cytogenetic findings, molecular mutations, blast percentage, blood counts, prior treatment, patient characteristics, and measurable residual disease. Instead of producing a static risk category, the model could continuously update the estimated disease trajectory as treatment information becomes available. If residual disease declines more rapidly than expected, the model could adjust its projections. If resistant disease emerges, the computational model could identify treatment scenarios associated with a higher probability of disease control.

Acute lymphoblastic leukemia presents another opportunity because treatment extends across multiple phases and requires careful management of relapse risk and toxicity. A digital twin could potentially simulate alternative treatment

schedules while considering disease response, patient characteristics, cumulative toxicity, and pharmacological exposure. Pediatric applications would require particularly careful validation because biological development, drug metabolism, and long-term treatment effects differ from those observed in adults.

In chronic leukemias, the longitudinal nature of treatment may make digital twins particularly useful. Patients can undergo repeated molecular monitoring over long periods, creating opportunities for models to learn from sequential measurements. The digital twin could potentially recognize changes in molecular disease burden before conventional clinical deterioration occurs and help clinicians evaluate whether treatment modification should be considered.

Lymphomas provide opportunities to integrate imaging with molecular and clinical data. Positron emission tomography, computed tomography, pathology, molecular testing, and treatment response measurements can collectively describe disease status. A digital twin could combine these inputs to estimate how disease burden might change under different therapeutic strategies. It might also help distinguish between residual abnormalities that represent active disease and changes associated with treatment effects, although such predictions would require rigorous clinical validation.

Multiple myeloma presents another strong use case because disease behavior can be monitored using multiple biomarkers over time. Serum markers, bone marrow measurements, imaging, cytogenetic information, and treatment history can provide longitudinal information. A digital twin could model the interaction between treatment pressure and clonal disease evolution. It could potentially help estimate when resistant subclones are becoming more prominent and identify situations in which a different therapeutic approach may be worth considering.

These applications remain primarily a research vision rather than established routine clinical practice. Reviews of digital twin research in oncology have identified substantial potential but also significant heterogeneity in methods and evidence quality. Many existing models rely on limited or synthetic datasets, while relatively few have demonstrated continuous real-time updating with robust prospective validation. Consequently, the future value of digital twins in hematology will depend not simply on technological sophistication but on whether their predictions consistently improve real clinical decisions and patient outcomes.

Treatment Simulation And Adaptive Therapy

One of the most important potential advantages of digital twins is the ability to simulate alterna-

tive treatment strategies before they are applied to the patient. Conventional clinical decision-making relies heavily on clinical trials, guidelines, physician experience, population-level evidence, and individual patient characteristics. These sources are essential, but they cannot fully predict the response of every individual. A digital twin could provide an additional layer by asking computationally what might happen if several different treatment strategies were applied to a particular patient.

In hematological cancer, treatment simulation could include comparisons between different drug combinations, treatment intensities, maintenance strategies, transplantation approaches, or cellular therapies. The model could estimate several outcomes simultaneously. These might include disease response, probability of relapse, treatment toxicity, expected duration of remission, and potential effects on quality of life.

Adaptive therapy is particularly relevant because hematological malignancies can change during treatment. A patient who responds exceptionally well may not need exactly the same strategy as a patient whose disease is resistant. A digital twin could be updated after each important clinical measurement and recalculate future scenarios. The approach would therefore move from a fixed treatment plan toward a continuously informed treatment pathway.

For example, suppose a patient with leukemia

begins induction therapy. Initial genomic information and clinical characteristics could be used to construct the first version of the digital twin. After several days or weeks, laboratory measurements and disease-response information would be incorporated. The model could then revise its projections. Following bone marrow assessment and minimal residual disease testing, the digital twin could again update the expected risks and benefits of potential next steps.

This concept could also be useful for managing treatment toxicity. Hematological cancer therapies can produce profound effects on blood cell production, infection risk, organ function, and immune responses. A digital twin that includes patient-specific toxicity information could simulate whether a proposed treatment strategy is likely to produce unacceptable adverse effects. The objective would be to balance disease control against treatment burden rather than optimizing only one outcome.

Another potential application involves cellular and immune-based therapies. The effectiveness of treatments such as cellular immunotherapies can depend on complex interactions between malignant cells and the patient's immune system. A digital twin could potentially integrate disease burden, immune characteristics, treatment history, and response patterns to estimate the likelihood of response or complications. Such models could become increasingly relevant as

cellular therapies expand across hematological malignancies.

Digital twins could also support clinical trial design. Researchers could use computational cohorts to explore eligibility criteria, treatment scenarios, and potential outcomes before conducting expensive clinical studies. Current oncology reviews identify clinical trial simulation and drug development as important potential applications of digital twin technology.

Nevertheless, simulation should never be confused with certainty. A digital twin does not literally reproduce every biological process occurring inside a patient. Its predictions are conditional on the quality of available data and the validity of the underlying models. Therefore, outputs should be communicated as probabilities and scenarios rather than definitive forecasts.

Artificial Intelligence And Multi-Omics Integration

Artificial intelligence will likely be one of the central technologies enabling advanced digital twins for hematological cancers. Hematology generates extremely large and heterogeneous datasets, including genomic sequences, transcriptomic profiles, proteomic measurements, flow cytometry results, pathology images, radiological images, blood counts, treatment histories, and longitudinal clinical observations.

Human clinicians cannot independently integrate all of these variables at high dimensionality. AI can help identify patterns across these datasets and transform them into clinically meaningful predictions.

Multi-omics integration is especially important because cancer is not determined by a single molecular feature. Genomic alterations can influence transcription, protein expression, cellular behavior, and treatment sensitivity. A digital twin could combine these layers with clinical and physiological information. The result would be a more comprehensive representation of the disease than a model based only on mutation status.

Machine learning could be used to estimate the probability of treatment response, relapse, or toxicity. Deep learning could analyze pathology or imaging data. Natural language processing could extract clinically important information from medical records. Time-series models could analyze how biomarkers change over weeks or months. Reinforcement learning approaches could potentially investigate sequential treatment strategies, although their clinical use would require particularly strong safeguards.

One promising direction is the integration of mechanistic biology with data-driven AI. Purely data-driven models can detect correlations without necessarily understanding biological causality. Mechanistic models, in contrast, can in-

corporate assumptions about cell growth, drug action, immune interactions, or disease evolution but may struggle with the complexity of real-world patient data. Combining the two approaches could provide models that are both more flexible and more biologically constrained. Research in oncology increasingly highlights mathematical modeling and AI as complementary tools for understanding treatment response and improving therapeutic delivery.

The digital twin could also become a platform for continuous learning. Each new patient observation could contribute information that improves the patient's individual model while potentially informing population-level models. This creates a feedback system in which clinical experience gradually improves computational predictions. However, safeguards would be necessary to prevent biased or poor-quality data from reinforcing incorrect conclusions.

Explainability is another major consideration. Clinicians need to understand why a digital twin predicts that one treatment strategy is preferable to another. A system that simply reports that treatment A has a higher predicted probability of success may be insufficient. It should ideally identify the major factors driving the prediction, distinguish established evidence from model inference, and communicate the uncertainty surrounding the estimate.

AI is already becoming increasingly relevant to

oncology regulation and drug development. The FDA established an Oncology Artificial Intelligence Program to improve understanding of AI methodologies and their application in cancer drug development. This growing regulatory interest suggests that AI-supported oncology systems will increasingly need formal standards for validation, monitoring, transparency, and safety.

Clinical Implementation And Personalized Decision-Making

For digital twins to become clinically useful, they must fit naturally into the workflow of hematologists, oncologists, pathologists, radiologists, pharmacists, nurses, and other members of the multidisciplinary care team. A technically impressive model that requires extensive manual data entry or produces results too late to influence treatment will have limited practical value.

The first stage of implementation would involve automated data collection. Laboratory results, molecular testing, imaging findings, medication records, and clinical observations should ideally flow into the digital twin through secure interoperable systems. Manual entry should be minimized because it creates additional workload and increases the risk of errors.

The second stage would involve model generation and updating. At diagnosis, the system could create an initial digital representation of

the patient. As new data arrive, the model would update its estimates. The interface could present a longitudinal view showing disease burden, treatment exposure, response trajectory, predicted risks, and areas of uncertainty.

The third stage would involve decision support. Rather than prescribing treatment automatically, the digital twin could present several evidence-informed scenarios. For example, it might show that one treatment has a higher estimated probability of disease control but also a higher predicted toxicity burden, while another approach has a lower predicted response but may be more suitable for a patient with particular clinical constraints.

This structure would preserve physician oversight. Digital twins should function as decision-support systems rather than autonomous decision-makers. The final treatment decision must account for factors that may not be fully captured in the model, including patient preferences, social circumstances, treatment accessibility, clinician judgment, and values concerning quality of life.

Patient involvement is also important. A digital twin could potentially provide patients with understandable visualizations of disease progression and treatment scenarios. However, this information must be presented carefully. Predictive probabilities can be emotionally difficult to interpret, particularly when they concern

relapse or survival. Communication should emphasize that computational predictions are estimates rather than individual certainties.

Clinical validation should occur before widespread adoption. A model might perform well retrospectively but fail when applied to patients from a different institution or population. Prospective studies should determine whether digital twin guidance improves outcomes compared with existing clinical decision-making. Relevant outcomes could include survival, relapse rates, treatment toxicity, hospitalization, quality of life, cost, and patient satisfaction.

Regulatory oversight will also become increasingly important. The FDA regulates AI-enabled medical devices using a risk-based approach and considers safety and effectiveness across the product lifecycle. Digital twins that influence diagnosis or treatment may therefore require careful consideration of intended use, validation, monitoring, software changes, and accountability.

Challenges, Ethics, And Data Governance

Despite their potential, digital twins face substantial scientific, clinical, ethical, and technological barriers. One of the most fundamental challenges is data quality. A digital twin is only as reliable as the information used to construct and update it. Incomplete records, inconsistent

laboratory measurements, differences in sequencing platforms, missing treatment data, and variation between hospitals can reduce model reliability.

Hematological cancers also present a biological challenge because malignant cell populations evolve. A digital twin created at diagnosis may become inaccurate if the disease acquires new mutations or develops resistant clones. The system therefore needs continuous updating rather than one-time construction. This is one reason digital twins are conceptually different from static risk calculators.

Generalizability is another problem. A model trained using data from one hospital or geographic population may not perform equally well in another setting. Differences in ethnicity, healthcare systems, treatment protocols, diagnostic practices, supportive care, and patient characteristics can influence predictions. External validation across multiple institutions and populations should therefore be a fundamental requirement.

Privacy represents another major concern. Digital twins may combine highly sensitive genomic, clinical, behavioral, and longitudinal information. Genomic data are particularly sensitive because they can provide information about biological relationships and potentially affect family members. Strong cybersecurity, access controls, encryption, consent processes, and

governance frameworks will be necessary.

There is also a risk of algorithmic bias. If training datasets underrepresent particular populations, the digital twin may provide less accurate predictions for those groups. A model could therefore unintentionally widen health disparities rather than reduce them. Fairness testing should be incorporated into development and monitoring rather than treated as an afterthought.

Another concern is automation bias. Clinicians may place excessive trust in a computational recommendation because it appears objective or technologically sophisticated. This could be dangerous when the underlying model is uncertain or wrong. Digital twin interfaces should therefore display uncertainty and encourage critical clinical review.

Accountability must also be clearly defined. If a physician follows a digital twin recommendation and the patient experiences an unexpected adverse outcome, responsibility cannot simply be assigned to the algorithm. Developers, healthcare institutions, clinicians, and regulators will need clearly defined roles.

The current evidence base also remains immature. Reviews have identified challenges involving data integration, model validation, scalability, privacy, and ethical governance. Many proposed applications remain experimental, and evidence demonstrating direct improvements in patient outcomes is still limited.

For these reasons, the development of digital twins should be accompanied by transparent governance. Patients should understand how their information is used, clinicians should understand the limitations of model predictions, and institutions should monitor performance after deployment. Digital twins should be treated as continuously evolving clinical technologies rather than finished products.

Future Outlook And Conclusion

The future of cancer treatment may increasingly involve a combination of biological experimentation, artificial intelligence, mathematical modeling, and continuous patient monitoring. Digital twins could become an important component of this emerging ecosystem, particularly in hematological cancers where disease biology can be measured repeatedly through blood, bone marrow, molecular, imaging, and clinical assessments.

A mature hematological cancer digital twin could begin with a patient's diagnostic profile and progressively incorporate every major clinical observation. Genomic data could describe the molecular landscape. Flow cytometry could characterize abnormal cell populations. Minimal residual disease testing could provide sensitive measurements of treatment response. Imaging could contribute information about disease distribution. Laboratory testing could monitor

physiological status. Treatment records could establish exposure history. Patient-reported outcomes could describe symptoms and quality of life. Artificial intelligence and mechanistic models could then combine these observations into an evolving computational representation.

The most important development would be the transition from static prediction to dynamic decision support. Instead of asking only whether a patient belongs to a high-risk or low-risk category, clinicians could ask how the patient's projected course changes under different treatment scenarios. This could support more individualized decisions throughout the entire treatment pathway.

Digital twins may also contribute to a new generation of clinical trials. Virtual patient populations could help researchers investigate trial designs, estimate likely outcomes, identify suitable patient subgroups, and explore treatment combinations before moving into large clinical studies. The technology may eventually help connect clinical trials with routine care by identifying patients whose digital profiles suggest that they could benefit from experimental approaches.

However, the promise of digital twins should not lead to unrealistic expectations. Current evidence indicates that oncology digital twins remain an emerging field with substantial methodological and translational challenges. A 2026 review identified applications across treatment

selection, drug development, immuno-oncology, radiotherapy, and survivorship, while emphasizing persistent problems involving data integration, validation, scalability, and ethical governance. The technology therefore requires rigorous clinical testing before it can be considered a standard component of hematological cancer treatment.

The next stage should focus on prospective validation, interoperability, transparent model development, and meaningful clinical outcomes. Researchers should determine not only whether digital twins can make accurate predictions but also whether using those predictions actually improves survival, reduces toxicity, improves quality of life, or makes healthcare more efficient.

Ultimately, the value of a digital twin will depend on its ability to connect complex biological information with practical clinical decisions. The objective is not to create a perfect virtual copy of a patient, which may be impossible, but to create a useful computational representation that becomes increasingly informative as new evidence is collected.

For patients with leukemia, lymphoma, multiple myeloma, and other hematological malignancies, this approach could support a more adaptive model of care. Instead of relying primarily on population averages and isolated clinical measurements, future treatment could

be guided by a continuously updated representation of the individual's disease, treatment response, biological characteristics, and clinical needs. If validated responsibly, digital twins could therefore become an important component of next-generation precision oncology, helping clinicians move toward treatment strategies that are more predictive, adaptive, individualized, and evidence informed.

2. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN ORAL CANCERS

Background

Cancers of the lip and mouth remain a significant global health problem and rank among the more common malignancies worldwide, standing as roughly the sixteenth most frequently diagnosed cancer overall. When considered within the broader category of head and neck cancers, the disease is even more prominent, representing the sixth most common malignancy globally. According to the most recent Global Burden of Disease estimates, the number of new cases reached approximately 422,000 in 2021, more than double the figure recorded in 1990, while the age-standardized incidence rate has continued its slow but steady rise. In 2022, close to 390,000 new diagnoses and more than 188,000 deaths were reported throughout the world. The burden of this cancer is not evenly distributed: Asia alone accounts for the majority of cases, men are affected more than twice as often as women, and incidence varies considerably between regions according to local habits and socioeconomic conditions. Tobacco smoking, alcohol consumption, and chewing tobacco or betel quid are among the most important

modifiable risk factors, contributing substantially to the global disease burden. Importantly, a considerable proportion of these cancers, by some estimates close to half, are preventable, which underscores both the scale of the missed opportunity and the value of earlier detection.

Despite considerable research efforts, clinical outcomes have improved only modestly. A substantial proportion of cases are detected at an advanced stage, and late diagnosis is one of the strongest predictors of poor prognosis; reported five-year survival generally remains between 40 and 60 percent. The influence of timing is striking, with early-stage disease associated with survival above 70 percent, whereas advanced-stage disease falls to little more than a third. The standard treatment options, including surgery, radiotherapy, and chemotherapy, increasingly complemented by immunotherapy, have been continuously refined, yet the overall prognosis has changed remarkably little over the past several decades. A further obstacle is the wide variability in how individual patients respond to identical treatment, driven largely by differences in tumor biology and genetic background. Such heterogeneity limits the value of standardized, one-size-fits-all protocols and reinforces the need for strategies tailored to each patient.

These limitations have accelerated a shift toward precision and personalized oncology, in which digital technologies and artificial intelligence are

assuming an increasingly central role. One of the most promising of these innovations is the digital twin. The digital twin concept was originally developed in engineering and industry. It is a computational model of a specific physical system that is continuously linked to that system, constantly updated with new data, and used to forecast its behavior and guide intervention. In clinical settings, a patient's digital twin combines multiple sources of information, including genetic profiles, tumor imaging, and clinical history. It is a dynamic virtual model that simulates disease progression and predicts the likely response to different therapeutic strategies before treatment is delivered. Interest in this approach has grown rapidly in recent years, propelled by the wider availability of large-scale patient data and by major advances in machine learning and computational modeling. In oncology, this paradigm offers a route toward safer, more precise, and more individualized cancer care.

This chapter presents a narrative review of the emerging role of digital twins in the next-generation treatment of oral cancers. It describes the conceptual framework and architecture of medical digital twins, reviews the data sources and enabling technologies needed for their development, surveys their potential clinical applications in oral cancer, and considers the principal challenges that must be resolved before this technology can be incorporated into routine

clinical practice.

Oral squamous cell carcinoma (OSCC) remains one of the most important malignancies in oral and maxillofacial oncology. Although surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy have improved the management of oral cancer, treatment outcomes are still highly variable. Patients with similar clinical stages may show very different patterns of treatment response, recurrence, survival, toxicity, and functional recovery. This variation reflects the biological complexity of OSCC, including differences in tumor genetics, immune microenvironment, local invasion, nodal spread, and patient-related factors.

In recent years, precision oncology has attempted to move cancer care beyond conventional staging systems toward more individualized treatment decisions. Within this context, the concept of the digital twin has gained increasing attention. A medical digital twin can be described as a dynamic, patient-specific computational model that integrates clinical, imaging, pathological, molecular, and longitudinal data to represent an individual patient and simulate possible disease or treatment trajectories. In oncology, digital twins are being discussed as tools that may support treatment selection, response prediction, toxicity estimation, adaptive therapy, and follow-up planning.

However, digital twins in oral cancer should be discussed with caution. At present, fully developed and clinically validated digital twins specifically designed for OSCC are not part of routine clinical practice. Most available evidence comes from broader oncology, head and neck cancer, and oral cancer studies using artificial intelligence, radiomics, digital pathology, genomics, multi-omics, and treatment response prediction models. These studies can be considered important building blocks for future oral cancer digital twins, but they do not yet represent complete patient-specific digital twin systems.

Therefore, this chapter reviews digital twins in oral cancer as an emerging framework for next-generation personalized treatment. Evidence from head and neck cancer is used where oral cancer-specific evidence is limited because oral cancer shares many clinical, anatomical, imaging, and molecular features with other head and neck squamous cell carcinomas.

Concept of Digital Twins in Oncology

The term “digital twin” refers to more than a simple prediction model. A conventional model may estimate prognosis or treatment response based on selected baseline variables. In contrast, a digital twin is expected to be dynamic, continuously updated, and individualized. In cancer

care, this means that a digital twin could combine patient data before, during, and after treatment to predict how a tumor may behave and how the patient may respond to different therapeutic options.

An oncology digital twin may include several layers of information. The first layer is the clinical layer, including tumor stage, site, histological findings, comorbidities, performance status, and previous treatment history. The second layer includes imaging and pathology data, such as CT, MRI, PET/CT, ultrasound, histopathology slides, and radiomics features. The third layer includes biological and molecular data, including genomics, transcriptomics, proteomics, immune markers, and liquid biopsy findings. Finally, the computational layer uses machine learning, mechanistic modeling, radiomics, radiogenomics, or multi-omics integration to generate predictions that may assist clinical decision-making.

In oral cancer, a digital twin could theoretically help answer clinically relevant questions. For example, it may estimate whether a patient is more likely to benefit from surgery alone or multimodal therapy, whether adjuvant radiotherapy should be intensified, whether immunotherapy is likely to be effective, or whether recurrence risk is increasing during follow-up. Still, these applications remain mostly investigational. The

current literature supports the potential of digital twins in oncology, but clinical translation in OSCC requires much stronger validation.

Why Digital Twins Matter in Oral Cancer

The main reason digital twins are relevant to oral cancer is the heterogeneity of the disease. OSCC is not a single uniform condition. Tumors differ in anatomical behavior, invasion pattern, molecular profile, immune activity, and sensitivity to treatment. Large molecular studies in head and neck squamous cell carcinoma have demonstrated substantial genomic heterogeneity, supporting the need for more personalized approaches.

Current treatment planning is largely based on clinical examination, imaging, histopathology, TNM staging, surgical judgment, and multidisciplinary discussion. These elements remain essential, but they do not always capture the full biological behavior of the tumor. A patient-specific digital twin could potentially combine these conventional data with radiomics, pathology AI, genomic alterations, immune markers, and longitudinal monitoring to provide a more complete view of the disease.

This is particularly important because oral cancer treatment often requires balancing survival with function. Surgery and adjuvant therapy

may affect speech, swallowing, mastication, facial appearance, and quality of life. A digital twin may eventually help clinicians compare different treatment scenarios and estimate not only oncological outcomes, but also toxicity and functional consequences.

The most relevant current example from head and neck cancer is the DITTO system, a visual digital twin designed to model treatment outcomes and toxicity trade-offs over time. Although this model is not limited to oral cancer, it demonstrates how digital twin thinking can be applied to complex head and neck oncology decisions. It also shows why oral cancer is a logical field for future digital twin development.

Data Sources for Oral Cancer Digital Twins

A useful oral cancer digital twin would depend on high-quality, multimodal data. Clinical data form the foundation. These include age, sex, smoking and alcohol exposure, tumor site, TNM stage, depth of invasion, nodal status, margin status, extracapsular spread, comorbidities, treatment details, and follow-up outcomes.

Imaging is another central component. CT, MRI, PET/CT, and ultrasound can provide information about tumor size, local invasion, nodal disease, and anatomical relationships. Radiomics allows quantitative features to be extracted

from images and may capture aspects of tumor heterogeneity that are not visible to the naked eye. In head and neck cancer, radiomics has been explored for survival prediction, HPV status, radiosensitivity, prognosis, and treatment response. In OSCC, CT-based radiomics has shown potential for predicting immunotherapy response, and MRI radiomics has been linked with immune gene-expression signatures. These studies suggest that imaging may become one of the most important bridges between the real patient and the virtual model.

Digital pathology is also highly relevant. Histopathological slides contain rich information about tumor architecture, invasion pattern, stromal reaction, and immune infiltration. AI-based pathology models may extract features that are difficult to quantify manually. For example, a recent digital pathology study showed that AI could help predict progression from oral potentially malignant lesions to OSCC. This indicates that pathology-based models may contribute not only to treatment planning, but also to early detection and surveillance.

Molecular data are equally important. Genomics and multi-omics can provide insight into tumor biology, immune activity, and potential therapeutic vulnerabilities. In OSCC and head and neck cancer, multi-omics integration may improve risk stratification and immunotherapy

prediction. Liquid biopsy may also play a role by allowing repeated and minimally invasive monitoring of tumor-derived signals over time. This longitudinal updating is essential because a true digital twin should change as the patient's condition changes.

Applications in Personalized Treatment Planning

Surgical Planning

Surgery is still the cornerstone of treatment for many patients with oral cancer. A digital twin could potentially help surgeons plan resection margins, predict soft-tissue changes, evaluate reconstructive options, and estimate functional consequences. In head and neck surgery, an AI-directed digital twin has been developed to measure soft-tissue shift, showing that digital twin approaches may help improve surgical modeling and navigation.

For oral cancer, this could be especially useful because treatment often involves anatomically complex areas such as the tongue, floor of mouth, mandible, buccal mucosa, and oropharyngeal border regions. However, surgical digital twins in oral cancer remain experimental and should not yet be considered standard clinical tools.

Radiotherapy Optimization

Radiotherapy is one of the most realistic areas for digital twin development because it already depends on imaging, dose modeling, tumor volume definition, organ-at-risk protection, and adaptive planning. A radiotherapy-oriented digital twin could integrate pretreatment imaging, pathology, clinical risk factors, and early response indicators to guide dose adaptation or predict toxicity.

Several head and neck cancer studies support this direction. Quantitative ultrasound radiomics has been used to assess radiosensitivity before treatment, and multimodal models combining imaging, clinical data, and pathology have shown value in predicting radiotherapy response. These findings suggest that future oral cancer digital twins may help personalize radiotherapy, although prospective validation is still required.

Systemic Therapy and Immunotherapy

Digital twins may also help personalize chemotherapy, targeted therapy, and immunotherapy. In theory, a digital twin could combine molecular alterations, immune biomarkers, radiomics, previous treatment response, and toxicity risk to estimate which systemic treatment is most suitable for a particular patient.

This is especially relevant for immunotherapy,

where only a subset of patients responds. PD-L1 expression is clinically useful but incomplete as a biomarker. Additional information from radiomics, immune gene signatures, tumor microenvironment analysis, and multi-omics may improve prediction. In OSCC, CT-based radiomics has been used to predict immunotherapy response, and MRI radiomics has been associated with immune gene-expression profiles. These studies provide direct oral cancer-related evidence, but they still need external validation before they can guide routine clinical care.

Follow-up and Recurrence Monitoring

Follow-up is another promising area for digital twins. Oral cancer recurrence risk is not static; it changes over time according to tumor biology, treatment response, symptoms, imaging findings, and molecular signals. A digital twin could be updated during follow-up and may help identify patients at higher risk of recurrence.

Liquid biopsy is particularly relevant in this setting because it may provide repeated, minimally invasive information about residual disease or recurrence. AI-based pathology models may also help identify high-risk premalignant lesions or patients who need closer surveillance. In the future, a follow-up digital twin could combine clinical examination, imaging, pathology, and

molecular monitoring to support more personalized surveillance strategies.

Integration with AI, Radiomics, and Multi-Omics

Artificial intelligence is likely to be the engine of many oral cancer digital twins. AI can help process large and complex datasets, including imaging, pathology, clinical variables, and molecular profiles. Radiomics can convert medical images into quantitative data, while digital pathology can extract detailed tissue-level features. Multi-omics can add deeper biological information about tumor behavior and treatment sensitivity.

The most promising direction is not to use these tools separately, but to integrate them. For example, a model that combines clinical data, CT or MRI radiomics, histopathology, genomic alterations, and immune markers may provide a more realistic representation of the patient than any single data source alone. Recent OSCC research supports this idea. Multimodal AI-based pathogenomics has improved survival prediction in OSCC by combining clinical, genomic, and pathology data. Similarly, radiogenomic work in OSCC suggests that imaging features may reflect underlying immune biology.

These studies are important because they show how the components of a future digital twin

are beginning to appear in oral cancer research. Nevertheless, they are still mainly predictive models. To become true digital twins, they must be connected to longitudinal patient data, updated over time, validated externally, and tested in clinical decision-making.

Challenges and Clinical Translation

Despite its promise, digital twin technology faces several barriers in oral cancer. The first is data quality and integration. Oral cancer data are often scattered across clinical records, radiology systems, pathology archives, molecular laboratories, and follow-up databases. Without standardized and interoperable data, building reliable digital twins is difficult.

The second major challenge is validation. Many AI and radiomics models show good performance in retrospective datasets but may not work equally well in different hospitals, scanners, populations, or treatment protocols. Digital twins require even stronger validation because they may influence high-risk clinical decisions. Verification, external validation, uncertainty estimation, interpretability, and biological plausibility are essential before clinical use.

Ethical and governance issues are also important. Digital twins require sensitive patient-specific data, including imaging, genomic infor-

mation, pathology, and longitudinal outcomes. This raises questions about consent, privacy, cybersecurity, data ownership, algorithmic bias, and responsibility for clinical decisions. Privacy-preserving approaches such as distributed learning may help support multicenter collaboration while reducing direct data-sharing risks.

Finally, digital twins must demonstrate clinical utility. A model is not useful simply because it predicts an outcome. It must improve treatment selection, reduce unnecessary toxicity, support better survival, improve quality of life, or make follow-up more effective. For OSCC, this will require prospective studies and eventually clinical trials comparing digital twin-assisted care with standard multidisciplinary treatment planning.

Future Perspectives

The future of oral cancer digital twins will probably be modular. Early systems may focus on one task, such as radiotherapy response prediction, immunotherapy selection, surgical simulation, recurrence monitoring, or malignant transformation risk assessment. Over time, these modules could be integrated into a broader patient-specific platform.

Near-term progress will depend on multicenter datasets, standardized imaging and pathology workflows, integration of genomics and immune profiling, liquid biopsy monitoring, explainable

AI, and clinically meaningful endpoints. The strongest future digital twins will not replace clinicians, but may support multidisciplinary decision-making by providing patient-specific simulations and risk estimates.

For now, digital twins should be described as an emerging and promising direction rather than an established clinical reality in oral oncology. Their value will depend on whether they can improve real patient outcomes in carefully designed clinical studies.

Conclusion

Digital twins have the potential to transform oral cancer care by integrating clinical, imaging, pathology, genomic, multi-omics, treatment-response, and follow-up data into dynamic patient-specific models. They may eventually support surgical planning, radiotherapy optimization, systemic therapy selection, immunotherapy response prediction, recurrence monitoring, and personalized surveillance.

However, fully validated digital twins for oral cancer are not yet available in routine clinical practice. Current evidence mainly consists of conceptual oncology frameworks, head and neck cancer digital twin-like systems, and oral cancer studies using AI, radiomics, digital pathology, liquid biopsy, and multi-omics. These studies provide the foundation for future development,

but further validation, ethical governance, data integration, and prospective clinical trials are necessary before digital twins can become part of standard oral cancer treatment.

3. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN NEUROLOGICAL CANCERS

Background

Neurological cancers, particularly primary brain and central nervous system tumors, represent some of the most complex malignancies encountered in modern oncology. Glioblastoma, diffuse gliomas, meningiomas, medulloblastomas, ependymomas, brain metastases, and other intracranial tumors differ substantially in their molecular characteristics, anatomical distribution, growth patterns, treatment sensitivity, and clinical trajectories. Their management is further complicated by the unique biological characteristics of the nervous system, including the blood-brain barrier, the specialized tumor microenvironment, neuronal and glial interactions, restricted drug penetration, and the potential for treatment-related neurological impairment. Consequently, conventional approaches based primarily on histopathological classification, molecular biomarkers, imaging, and population-level treatment evidence may not completely capture the dynamic characteristics of an individual patient's disease.

The development of precision oncology has substantially changed the diagnosis and treatment of neurological cancers. Molecular profiling can identify clinically relevant alterations, while advanced magnetic resonance imaging, positron emission tomography, radiomics, liquid biopsy, and artificial intelligence can provide increasingly detailed information about tumor biology and treatment response. However, these technologies often generate separate streams of information. The challenge is to integrate these heterogeneous data sources into a coherent representation of the individual patient that can be continuously updated as the tumor evolves.

Digital twins provide a potential framework for addressing this challenge. A medical digital twin can be conceptualized as a dynamic computational representation of an individual patient that integrates clinical, biological, imaging, and longitudinal information to model the patient's current condition and potentially simulate future states. Rather than functioning as a static risk calculator, a digital twin is intended to evolve as new information becomes available. In oncology, this approach has attracted increasing interest because it may support personalized treatment selection, response prediction, treatment optimization, clinical trial design, and disease monitoring.

For neurological cancers, the digital twin could integrate magnetic resonance imaging, com-

puted tomography, positron emission tomography, pathology, molecular profiling, genomic and transcriptomic information, treatment history, neurological examination findings, corticosteroid exposure, radiotherapy parameters, systemic therapy, and patient-reported outcomes. Artificial intelligence could analyze these data to characterize tumor heterogeneity, estimate disease progression, identify treatment response patterns, and predict adverse outcomes. Mechanistic models could complement data-driven approaches by representing tumor growth, spatial invasion, treatment effects, and interactions between malignant cells and their surrounding environment.

The importance of this approach arises from the highly dynamic nature of neurological cancers. A tumor may change its molecular characteristics during treatment, develop resistant subclones, alter its microenvironment, or exhibit imaging changes that are difficult to distinguish from treatment-related effects. Pseudoprogression after chemoradiotherapy and radiation necrosis are important examples in which imaging abnormalities do not necessarily represent straightforward tumor progression. A digital twin could potentially integrate sequential imaging, clinical findings, molecular information, and treatment exposure to provide a more individualized interpretation of these changes.

The ultimate objective is not to replace

neurologists, neurosurgeons, neuro-oncologists, radiologists, or other specialists. Instead, digital twins could provide an advanced decision-support framework that allows clinicians to examine multiple treatment scenarios for a specific patient. This could facilitate a transition from static precision oncology toward dynamic precision care, in which treatment decisions are continuously adapted according to the evolving biological and clinical state of the tumor.

Digital Twin Architecture For Neurological Cancer Care

A digital twin for neurological cancer would require a multidimensional architecture capable of representing both the tumor and the patient in whom it develops. The physical patient would remain the primary biological system, while the digital twin would provide a computational representation that is continuously updated through clinical observations. This architecture would need to incorporate data acquisition, integration, computational modeling, synchronization, prediction, visualization, and clinical decision support.

Neuroimaging would represent one of the most important components. Magnetic resonance imaging can provide information about tumor location, size, shape, edema, necrosis, contrast enhancement, diffusion, perfusion, and metabolic characteristics. Advanced MRI techniques

can add information about tissue architecture and vascular behavior. Serial imaging can then provide temporal information about how these characteristics change during treatment. A digital twin could use automated image segmentation and radiomic analysis to convert these images into quantitative representations of tumor phenotype.

Pathology and molecular data would provide another major component. Histological classification alone may be insufficient to describe the biological behavior of a neurological tumor. Molecular alterations can influence prognosis and therapeutic sensitivity, while intratumoral heterogeneity may result in different subpopulations of cells responding differently to treatment. The digital twin could integrate genomic, transcriptomic, epigenomic, and proteomic information to create a more comprehensive representation of tumor biology.

Clinical information would also be essential. Age, functional status, neurological deficits, seizure history, comorbidities, medication use, treatment history, and patient-reported symptoms could influence both treatment selection and outcomes. Corticosteroid use, for example, can affect symptoms, imaging appearance, immune responses, and quality of life. These factors should therefore be incorporated rather than treated as independent variables outside the computational model.

The computational layer could consist of several complementary models. A tumor-growth model could estimate spatial and temporal progression. A machine learning model could predict treatment response. A pharmacokinetic and pharmacodynamic model could estimate drug exposure and biological effects. A radiotherapy model could represent dose distribution and its relationship with tumor control and normal-tissue injury. A probabilistic framework could quantify uncertainty when information is incomplete.

Synchronization would allow the digital twin to change when new clinical evidence becomes available. Following surgery, the model could incorporate pathological and molecular findings. After radiotherapy, it could incorporate treatment dose and fractionation. Following chemotherapy or targeted therapy, it could incorporate treatment exposure and response. Subsequent MRI examinations could update estimates of tumor burden and progression. The digital twin would therefore function as a longitudinal representation rather than a one-time assessment.

An effective interface would be necessary for clinical implementation. Physicians should be able to visualize tumor changes over time, review the major factors influencing predictions, compare treatment scenarios, and examine uncertainty. A digital twin should not simply provide a single prediction such as "progression likely." Instead, it should provide clinically inter-

pretable information about why progression is predicted, how confident the model is, and how alternative interventions might modify the expected trajectory.

This architecture could ultimately transform neurological cancer management from a sequence of isolated clinical decisions into an integrated computationally supported process. However, the quality of the digital twin would remain dependent on the quality, completeness, interoperability, and representativeness of the underlying data.

Applications In Gliomas And Glioblastoma

Gliomas provide one of the most important potential applications for digital twin technology because of their substantial molecular, spatial, and temporal heterogeneity. Glioblastoma is particularly challenging because it can infiltrate surrounding brain tissue, contain multiple cellular subpopulations, develop treatment resistance, and recur despite multimodal therapy. Standard treatment generally involves combinations of surgery, radiotherapy, systemic therapy, and supportive management, but outcomes remain highly variable.

A glioblastoma digital twin could begin with preoperative imaging and molecular information. MRI could define the visible tumor and surrounding abnormalities, while molecu-

lar profiling could provide information about tumor biology. Following surgical resection, postoperative imaging and pathological findings could be incorporated. The digital twin could then estimate residual tumor burden and simulate potential disease trajectories.

One important application would be modeling tumor growth and infiltration. Glioblastoma does not behave simply as a spherical mass that expands uniformly. Malignant cells can migrate through surrounding brain tissue, making complete surgical removal difficult. Mathematical models could potentially represent the spatial dynamics of tumor infiltration and identify regions at greater risk of microscopic disease. When combined with imaging and clinical data, these models could help explore how different treatment strategies might influence future tumor distribution.

Radiotherapy planning is another promising area. A digital twin could integrate tumor location, predicted infiltration patterns, functional brain regions, and treatment dose distributions. Computational simulations could then compare alternative radiotherapy plans according to predicted tumor control and normal brain exposure. This could potentially support more individualized treatment planning, particularly when tumors are located near eloquent neurological structures.

Treatment response monitoring is equally im-

portant. Following chemoradiotherapy, MRI abnormalities may reflect recurrent tumor, treatment-related inflammation, pseudoprogression, or radiation injury. A digital twin could combine serial imaging, clinical symptoms, treatment timing, and molecular information to estimate the probability that a new imaging abnormality represents active tumor. Artificial intelligence-based imaging models may contribute quantitative features that are difficult to assess visually.

At recurrence, the digital twin could be reconstructed using new molecular and imaging information. Recurrence may differ biologically from the original tumor because treatment creates selective pressure. A model that continues to rely on the original diagnostic profile may therefore become increasingly inaccurate. Continuous updating could allow the computational representation to reflect the new disease state.

Digital twins could also support experimental treatment selection. For patients with recurrent glioblastoma, clinicians frequently face several potential options with uncertain benefit. A computational model could compare candidate therapies according to the patient's molecular characteristics, previous treatments, predicted drug penetration, expected toxicity, and disease trajectory.

However, these applications require careful validation. Glioblastoma is biologically complex, and predictions based on retrospective datasets

may not generalize to individual patients. Furthermore, tumor heterogeneity means that a single biopsy may not fully represent the entire tumor. Future digital twins will therefore need methods capable of integrating spatially heterogeneous information and explicitly representing uncertainty.

Integration Of Imaging, Artificial Intelligence, And Multi-Omics

The value of digital twins in neurological cancers will depend heavily on the integration of multimodal data. Neuro-oncology generates large amounts of information, but these data types differ substantially in structure, resolution, timing, and biological meaning. MRI consists of high-dimensional spatial information, genomic sequencing provides molecular information, pathology describes cellular characteristics, and clinical records contain longitudinal observations. Artificial intelligence can provide the computational infrastructure required to integrate these heterogeneous sources.

Radiomics is particularly relevant because it can convert medical images into quantitative features describing tumor intensity, texture, shape, spatial relationships, and temporal changes. Deep learning can further identify imaging patterns that may not be captured by predefined radiomic measurements. When combined with molecular data, these approaches may allow the

digital twin to associate imaging phenotypes with underlying tumor biology.

Multi-omics integration can add another dimension. Genomic alterations can affect gene expression, protein activity, cellular metabolism, and treatment response. A digital twin could therefore represent the tumor as a network of interacting biological processes rather than a collection of independent biomarkers. This could be especially useful for tumors with substantial intratumoral heterogeneity.

Artificial intelligence could also extract information from unstructured clinical records. Natural language processing could identify treatment responses, neurological symptoms, adverse events, and historical disease characteristics from clinical notes. This would allow the digital twin to incorporate information that would otherwise remain inaccessible to structured databases.

Longitudinal modeling is another important capability. A neurological cancer is not defined only by its characteristics at diagnosis. Its trajectory is determined by how the tumor changes over time and how it responds to interventions. Time-series models could analyze sequential imaging, laboratory measurements, neurological assessments, and treatment events. The resulting model could estimate the probability of future progression or treatment response based on the trajectory rather than a single measurement.

Combining mechanistic models with artificial

intelligence may be particularly valuable. Machine learning can discover complex relationships within large datasets, but its predictions may be difficult to interpret and may fail when applied outside the population represented in its training data. Mechanistic models can impose biological structure, such as assumptions about tumor growth, treatment effects, and spatial invasion. A hybrid digital twin could therefore use AI to learn patient-specific parameters while maintaining biologically meaningful constraints.

This approach could also facilitate continuous learning. As new imaging and molecular data become available, the digital twin could update its estimates. However, continuous learning requires safeguards. A model should not automatically incorporate every new observation without quality assessment because errors, artifacts, or unusual cases could lead to inappropriate model adaptation.

Explainability is equally important. A clinician should be able to determine which factors are influencing the model's prediction. If the digital twin estimates a high probability of progression, it should identify whether the prediction is primarily driven by imaging changes, molecular characteristics, treatment history, or temporal patterns. Such transparency would help clinicians assess whether the output is clinically plausible.

Ultimately, multimodal AI integration could transform the digital twin from a conventional predictive algorithm into a comprehensive computational platform. The combination of imaging, pathology, molecular data, clinical information, and longitudinal observations could provide a more detailed representation of neurological cancer and its evolution.

Treatment Simulation And Adaptive Therapeutic Strategies

One of the most transformative potential applications of digital twins is treatment simulation. Current treatment guidelines are based largely on evidence from clinical trials and population-level outcomes. Although these studies provide essential information, they cannot perfectly predict the response of every individual patient. Digital twins could provide an additional computational layer by simulating different therapeutic scenarios for a specific patient.

In neurological cancers, treatment simulation could involve surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, tumor treating fields, and investigational treatments. The model could compare these options according to predicted tumor control, progression risk, toxicity, neurological function, and quality of life.

Surgical planning represents one potential application. A digital twin could integrate tumor

anatomy with information about functional brain regions and predicted tumor infiltration. It could then help simulate potential resection strategies. The objective would not be to automate neurosurgical decisions but to provide a quantitative framework for balancing maximal tumor removal against preservation of neurological function.

Radiotherapy could similarly be optimized through simulation. Different treatment plans could be evaluated according to predicted tumor control and exposure of healthy brain tissue. A digital twin could potentially account for changes in tumor geometry over time, allowing adaptive radiotherapy strategies to be explored.

Systemic treatment could also be modeled. For example, the digital twin could compare different drug combinations using molecular information, previous treatment exposure, predicted drug sensitivity, and patient-specific toxicity risks. Such simulations could become particularly valuable in recurrent disease, where standard treatment options may provide limited benefit.

Adaptive treatment would involve repeated model updating. After an intervention, new information would be incorporated into the digital twin, and future treatment scenarios would be recalculated. This creates a treatment cycle consisting of observation, computational updating, simulation, intervention, and reassessment.

Such a system could be especially valuable when treatment response is heterogeneous. A patient may show substantial tumor reduction in one region while another region remains stable or progresses. A conventional overall response measurement may not fully describe this situation. A digital twin could potentially model spatially distinct disease behavior and identify areas requiring alternative treatment strategies.

Patient preferences could also be incorporated into treatment simulation. Some patients may prioritize maximal survival, while others may place greater importance on preservation of cognitive function, independence, or quality of life. A digital twin could present different scenarios according to these priorities rather than assuming that all patients have identical treatment goals.

Importantly, treatment simulation must remain probabilistic. A computational prediction should never be interpreted as a guaranteed outcome. The biological system remains more complex than any computational representation, and unexpected events can occur. Therefore, the digital twin should support shared decision-making rather than replace it.

Clinical Implementation And Patient-Centered Decision-Making

Successful implementation of digital twins in neurological oncology will require close integra-

tion with existing clinical workflows. Neuro-oncology care is inherently multidisciplinary and can involve neurosurgeons, neurologists, neuro-oncologists, radiation oncologists, neuroradiologists, neuropathologists, medical oncologists, rehabilitation specialists, nurses, and palliative care professionals. A digital twin should therefore provide information that can be interpreted across specialties.

Automated data integration would be one of the first requirements. The system should ideally receive imaging, pathology, molecular, treatment, and clinical information through interoperable platforms. Manual data entry should be minimized because it can increase workload and introduce errors.

At diagnosis, the digital twin could generate a baseline representation. During treatment, it could receive updated information at predefined intervals. Following each major clinical event, the model could reassess disease status and future risks. A dashboard could display longitudinal changes in tumor characteristics, predicted progression, treatment exposure, and uncertainty.

The interface should prioritize clinically meaningful information. Excessive technical detail may make the system difficult to use. Instead, the clinician could be presented with a concise overview accompanied by access to detailed evidence supporting each prediction. The model

should also clearly distinguish observed data from computational inference.

Patient-centered decision-making would be another major component. Neurological cancer treatments can affect cognition, mobility, speech, vision, seizures, mood, and independence. Therefore, survival alone cannot represent the full value of treatment. A digital twin could potentially incorporate functional outcomes and patient-reported measures alongside tumor control.

For example, two treatment strategies might have similar predicted effects on tumor progression but substantially different risks of neurological impairment. A digital twin could present this tradeoff explicitly, helping clinicians and patients make decisions according to individual preferences.

Clinical validation should be prospective and multicenter. A model that performs well in one institution may fail elsewhere because of differences in imaging protocols, patient populations, molecular testing, treatment patterns, and clinical workflows. External validation should therefore be followed by prospective studies evaluating whether digital twin-guided decisions improve meaningful patient outcomes.

Important outcomes could include overall survival, progression-free survival, neurological function, cognitive outcomes, treatment toxicity, hospitalization, quality of life, and health-

care utilization. It would also be important to determine whether digital twins improve the efficiency of multidisciplinary decision-making.

Regulatory oversight will become increasingly relevant as these systems begin to influence clinical decisions. Developers will need to demonstrate analytical validity, clinical validity, reliability, cybersecurity, and appropriate performance monitoring. Models may also require continuous reassessment because changes in imaging technologies, treatment standards, and patient populations can affect their performance.

Ultimately, clinical implementation should follow a staged approach. Early systems could provide descriptive visualization and risk estimation. More advanced systems could provide treatment simulations. Highly autonomous treatment recommendations should only be considered after extensive evidence demonstrates safety, reliability, and clinical benefit.

Challenges, Ethical Considerations, And Future Directions

Despite their potential, digital twins for neurological cancers face substantial challenges. The first is data heterogeneity. MRI protocols differ between institutions, molecular testing platforms vary, and clinical records often contain incomplete information. These differences can reduce model generalizability. Standardization and interoperability will therefore be fundamen-

tal to successful implementation.

Another challenge is tumor heterogeneity. Brain tumors can contain multiple molecularly distinct cellular populations. A biopsy samples only a limited region, while imaging provides broader but less specific information. A digital twin must therefore represent uncertainty regarding the true biological state of the entire tumor.

Temporal evolution creates an additional challenge. Tumors can develop resistance under treatment pressure. A model created at diagnosis may become inaccurate months later. Continuous updating is therefore necessary, but continuous updating also creates opportunities for error accumulation.

Privacy and cybersecurity are major ethical concerns. Digital twins may contain highly sensitive medical and genomic information. Unauthorized access could expose information about disease status, genetic characteristics, treatment history, and future health risks. Robust governance, encryption, access controls, and transparent consent mechanisms will be required.

Algorithmic bias must also be addressed. If training datasets are derived primarily from selected populations or high-resource cancer centers, models may perform poorly in underrepresented groups. This could create disparities in access to accurate computational decision support. Multicenter and geographically diverse datasets should therefore be incorporated into development and validation.

Interpretability is another important consideration. Clinicians should not be expected to trust a prediction simply because it originates from an advanced AI system. Digital twins should provide understandable explanations, confidence estimates, and information about the data supporting each prediction.

There is also a risk of automation bias. If clinicians become overly dependent on computational recommendations, they may overlook clinically important information that the model cannot represent. Human oversight should therefore remain central to decision-making.

Future systems may become increasingly sophisticated through the combination of digital twins with foundation models, multimodal artificial intelligence, spatial transcriptomics, single-cell sequencing, advanced imaging, and wearable or home-monitoring technologies. This could allow digital twins to represent not only tumor biology but also functional status and patient experience.

Another important future direction is the development of virtual clinical trials. Digital twins could help construct computational patient populations that resemble real-world populations and allow researchers to investigate alternative trial designs. This could potentially improve trial efficiency and identify patient subgroups that are most likely to benefit from ex-

perimental treatments.
Digital twins may also support survivorship and rehabilitation. For patients who achieve long-term tumor control, the computational model could monitor neurological function, cognitive outcomes, endocrine complications, fatigue, and quality of life. Thus, the technology could extend beyond active cancer treatment and become a longitudinal platform for the entire cancer journey.

Conclusion

Digital twins represent an emerging approach with the potential to transform neurological cancer treatment from static, population-based decision-making toward dynamic and individualized therapeutic management. By integrating neuroimaging, pathology, molecular profiling, clinical information, treatment history, and longitudinal outcomes, a digital twin could provide a continuously updated computational representation of both the tumor and the patient.
The technology may be particularly valuable for glioblastoma and other complex brain tumors because these malignancies exhibit substantial spatial and molecular heterogeneity, evolve during treatment, and frequently generate diagnostic uncertainty during response assessment. Digital twins could potentially support surgical planning, radiotherapy optimization, treatment selection, response monitoring, recurrence management, toxicity prediction, and adaptive therapy.

Artificial intelligence will likely provide an important computational foundation for these systems. However, the most clinically useful digital twins will probably combine AI with mechanistic models, multimodal data integration, and explicit representation of uncertainty. Their purpose should be to enhance clinical reasoning rather than replace it.
The transition from research concept to routine clinical practice will require substantial evidence. Prospective validation, external testing, standardized data structures, interoperability, cybersecurity, fairness assessment, regulatory oversight, and transparent communication will be essential. Most importantly, future studies must demonstrate that digital twin use produces meaningful improvements in patient outcomes rather than merely achieving high predictive performance.
If these challenges can be addressed, digital twins could become a central component of next-generation neuro-oncology. They could allow clinicians to move beyond asking which treatment is generally effective for a particular tumor type and toward a more individualized question: which treatment strategy is most likely to provide the best balance of tumor control, neurological preservation, safety, and quality of life for this particular patient at this

particular stage of disease? This shift could represent an important step toward truly dynamic precision medicine in neurological cancers.

4. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN BREAST CANCERS

Background

Breast cancer is the world's second most frequently diagnosed cancer, with approximately 2.3 million new cases each year. In Western nations, the adoption of screening programs has led to more early diagnoses. Recently, non-wired, non-ionizing devices have emerged, and supine MRI has been suggested as a way to better match the patient's position during surgery. However, despite these advancements, standard tumor localization methods remain percutaneous, are frequently performed before surgery, are uncomfortable for patients, and are insufficiently precise. The National Academies describe a digital twin as a collection of virtual information models that replicate the structure, context, and behavior of a physical, engineered, or social system. These models are continuously updated with data from their real-world counterparts, possess predictive capabilities, and guide decisions that generate value. Crucially, the digital and physical versions interact bidirectionally.

By integrating genetic, biochemical, and lifestyle information, digital twins can support accurate screening and diagnosis and enable person-

alized treatment strategies. Coupled with cloud computing, artificial intelligence, and machine learning technologies, this digital counterpart is capable of interpreting and processing data, enabling advanced analysis and informed decision-making. In breast cancer, this strategy holds particular significance because of the disease's inherent biological heterogeneity, which results in variable therapeutic responses among patients with the same clinical diagnosis. A key advantage of digital twins is their capacity to forecast treatment response before therapy starts. Chemotherapy regimens can be virtually tested to estimate their effectiveness and likely outcomes.

Digital twins have been most effectively applied in the context of triple-negative breast cancer (TNBC), a particularly aggressive form with few targeted therapies available. A recent investigation involved the creation of MRI-based digital twins for TNBC patients undergoing neoadjuvant chemotherapy. By calibrating the model with imaging data specific to each patient, researchers achieved a promising level of accuracy in predicting pathological complete response. Notably, the digital twin also allowed for the simulation of various treatment schedules, helping to identify regimens that could enhance tumor response. This approach is clinically significant because it facilitates the optimization of

treatment plans prior to the commencement of therapy, rather than reacting to inadequate responses post-treatment.

A practical digital twin framework was created by researchers using data from 105 TNBC patients involved in the ARTEMIS clinical trial, all of whom underwent neoadjuvant chemotherapy. For each patient, a digital twin was employed to virtually evaluate 128 distinct chemotherapy scheduling options involving Adriamycin/Cytoxan-Taxol (A/C-T), achieving a prediction accuracy for pathological complete response (pCR) with an area under the curve of 0.82. The regimens optimized through digital twin simulations led to an increase in pCR rates of 20.95–24.76% when compared to conventional protocols. Importantly, the digital twins confirmed that administering A/C-T bi-weekly is more effective than a tri-weekly schedule, and that weekly or bi-weekly Taxol dosing is superior to tri-weekly administration, insights that can be immediately applied in clinical settings. This marks the first instance in which digital twins have demonstrated the potential for significant treatment enhancements through in silico drug testing. While advancements have been made, several key challenges persist. To routinely implement digital twins in clinical practice, it is essential to have access to high-quality longitudinal data, dependable computational methods,

and thorough validation processes. Breast cancer is a complex disease, influenced by genetic factors, the tumor's microenvironment, and the patient's treatment history, making it difficult for a single model to represent all aspects of patient biology. However, recent reviews highlight the significant potential of digital twins in oncology, including their application in treatment selection, radiotherapy planning, and adaptive care.

Breast cancer (BC) is a biologically and clinically heterogeneous disease, characterized by substantial variation at the histological, genomic, transcriptomic, and immunological levels. It remains one of the most frequently diagnosed malignancies among women worldwide and constitutes a substantial proportion of cancer-related morbidity and mortality. Although this malignancy is primarily diagnosed in older populations, particularly among women aged ≥65 years in high-income countries, recent epidemiological evidence indicates a rising burden among younger populations and increasingly diverse demographic groups. Taken together, these studies highlight the complex biological and clinical landscape of breast cancer, which underlies the limitations of uniform therapeutic paradigms and reinforces the need for more personalized, data-driven, and computationally informed approaches to its prevention, diagnosis, and treatment.

Despite substantial advances in diagnostic technologies and therapeutic interventions, achieving consistently optimal outcomes for individual patients remains a persistent challenge. The pronounced biological heterogeneity of breast cancer drives substantial inter-patient and intratumoral variability in treatment response, even within clinically comparable subgroups. Current therapeutic decision-making is still largely grounded in population-averaged evidence derived from clinical trials and standardized guidelines, which only partially reflect patient-specific disease dynamics. Consequently, the selection of optimal therapeutic regimens, including drug type, dosing, and scheduling, continues to represent a central unmet need in precision oncology.

Digital twin methodologies in medicine offer a potential shift from static, population-based models toward continuously updated, patient-specific computational representations. In this paradigm, cancer patient digital twins (CPDTs) are emerging as integrative frameworks that combine advances in computing, systems biology, and biomedical data science to construct in silico representations of individual patients. These models are designed to dynamically reflect molecular, physiological, imaging, and lifestyle-related states over time and under different therapeutic conditions. Within this framework, CPDTs support a continuous

lifecycle of simulation, prediction, and clinical feedback, enabling a more iterative model of shared decision-making in oncology. Operationally, the proposed CPDT architecture relies on the integration of multiscale and multimodal datasets, including proteomic and clinical profiles, imaging-derived biomarkers, and evidence from clinical trials and population-level studies, to support robust model training and validation. Recent evidence suggests that network-based digital twins generated using synthetic data can improve mortality prediction across multiple cancer types. The SynTwin framework demonstrated superior predictive performance over models based solely on real-patient data, particularly in large datasets with effective sample sizes exceeding critical thresholds. These findings highlight the potential of synthetic-data-based digital twins while emphasizing the importance of an adequate and effective sample size for achieving robust predictive performance.

In parallel, integrative modeling approaches that combine quantitative MRI with biologically based mathematical models have demonstrated strong patient-specific predictive capability in aggressive breast cancer subtypes. In triple-negative breast cancer (TNBC), MRI-derived imaging data integrated with mathematical representations of tumor cell movement, proliferation, and treatment-induced cell death

have enabled accurate prediction of neoadjuvant systemic therapy response. By capturing the spatiotemporal dynamics of tumor evolution during treatment, these models have demonstrated superior predictive performance compared with conventional imaging-based volumetric assessment, highlighting their potential to support personalized therapeutic decision-making. To ensure scalability, interoperability, and clinical equity, data acquisition and integration should adhere to FAIR (Findability, Accessibility, Interoperability, and Reusability) principles and incorporate sufficiently diverse populations, thereby reducing systematic bias and promoting equitable benefit across patient groups.

Despite these advances, several interdependent challenges continue to limit the development and clinical translation of CPDTs. At the data level, a key limitation is the availability of high-quality, multiscale datasets capable of capturing both healthy and diseased states while maintaining adequate representation across diverse populations. The heterogeneity of data sources, particularly when integrating legacy clinical records with emerging omics and imaging datasets, complicates harmonization and limits the construction of unified disease representations. From a modeling perspective, integrating data-driven approaches with mechanistic frameworks remains challenging, particularly

with respect to uncertainty quantification and standardized validation. Practical implementation is further constrained by limited access to interoperable datasets, computational workflows, and high-performance computing infrastructure. Ethical and regulatory considerations, including bias mitigation, stakeholder inclusion, and patient privacy protection, remain central to system design. In addition, the absence of harmonized regulatory frameworks for data governance and clinical deployment continues to slow translation into routine oncology clinical practice.

Collectively, these developments suggest that hybrid computational frameworks integrating mechanistic structure with data-driven learning may form a foundational pathway toward clinically actionable digital twin systems in precision oncology.

Among emerging technologies, digital twins have attracted growing attention. Originally developed for engineering applications, a digital twin is a virtual representation of a real system that is continuously updated using real-world data. Recent studies have highlighted its potential value in healthcare and precision medicine. In healthcare, a digital twin attempts to create a computational model of a disease by integrating information from multiple sources, including clinical features, imaging findings, genetic pro-

files, and treatment history.

Unlike traditional prediction models that often rely on population averages, digital twins aim to capture the characteristics of individual patients and explore how a disease may develop under different treatment conditions. Because breast cancer can vary substantially from one patient to another, digital twins offer an alternative approach by using patient information to examine how the disease may respond to different treatment strategies.

Choosing the right treatment has always been a major challenge in breast cancer care because patients with seemingly similar clinical features may respond differently to the same therapy. Therefore, digital twins can create a virtual representation of a patient's condition and allow different treatment options to be explored before treatment begins. This approach may help doctors choose the most appropriate treatment for each patient while avoiding unnecessary therapies and reducing adverse effects associated with treatment.

Digital twins can also help track changes in a patient's condition throughout the treatment process by incorporating newly available clinical information. This may provide doctors with a clearer understanding of disease progression and support treatment decisions that better reflect the needs of individual patients. Beyond

treatment selection, digital twins may also help researchers and clinicians better understand how breast tumors change over time. By combining imaging data with clinical and molecular information, these models can provide a more detailed picture of tumor behavior and disease progression. Such information may be useful for identifying patients who require closer monitoring and for detecting changes in treatment response at earlier stages. As more patient data become available, digital twins may improve the ability to anticipate disease outcomes and support timely clinical interventions.

Although the use of digital twins in breast cancer is still developing, recent progress in artificial intelligence, machine learning, and biomedical informatics has increased interest in this technology. Several challenges remain, including data integration, model validation, patient privacy, and regulatory approval. Despite these limitations, digital twins have the potential to improve treatment planning and support more personalized approaches to breast cancer care. As more research becomes available, they may play an increasingly important role in helping doctors make treatment decisions and improve patient outcomes.

Digital Twin Architecture For Breast Cancer

A clinically meaningful breast cancer digital twin would require an architecture capable of integrating multiple data sources and representing the patient across different stages of diagnosis and treatment. The physical patient would remain the biological system of interest, while the digital twin would function as a continuously updated computational representation. Its architecture would include data acquisition, integration, computational modeling, synchronization, prediction, visualization, and clinical decision support.

Breast imaging would represent one of the principal components. Mammography provides information about masses, calcifications, asymmetry, and architectural distortion, while ultrasound can characterize lesions according to their morphology and vascular characteristics. Magnetic resonance imaging provides additional information about tumor extent, enhancement patterns, vascularity, and multifocal or multicentric disease. Sequential imaging can also provide information about treatment response. Artificial intelligence can extract quantitative features from these modalities and incorporate them into the digital twin.

Pathology represents another critical component. Histological type, tumor grade, lymphovascular invasion, proliferation markers, receptor expression, and other pathological characteristics can provide important information about disease behavior. Digital pathology could allow computational models to analyze whole-slide images and identify morphological features associated with prognosis or treatment response. Integration of pathology with radiological and molecular information could create a more comprehensive representation of tumor biology.

Molecular information would further enhance the digital twin. Genomic sequencing can identify alterations that influence prognosis or treatment selection. Transcriptomic information can characterize biological pathways and molecular subtypes. Circulating tumor DNA may provide a minimally invasive method for monitoring molecular disease burden over time. These data could be incorporated into the digital twin as dynamic biomarkers rather than one-time observations.

Clinical information should also be incorporated. Age, menopausal status, family history, body composition, comorbidities, previous cancer treatment, medications, reproductive characteristics, and functional status may influence treatment decisions. Patient-reported outcomes could provide information about symptoms, fatigue, pain, treatment burden, and quality of life.

The computational layer could contain several interconnected models. Machine learning could estimate recurrence or treatment response. Deep

learning could analyze medical images and digital pathology. Pharmacokinetic and pharmacodynamic models could represent drug exposure and response. Mechanistic models could describe tumor growth or treatment effects. Probabilistic models could represent uncertainty when data are incomplete.

Synchronization would be essential because breast cancer changes over time. A new biopsy could alter the molecular representation. A reduction in tumor size during neoadjuvant treatment could modify the predicted probability of pathological response. Detection of circulating tumor DNA after treatment could alter estimates of residual disease. At recurrence, new molecular findings could substantially change the digital twin.

The interface should present information in a clinically meaningful way. Rather than displaying numerous independent predictions, the system could show a longitudinal disease trajectory, major biological characteristics, predicted outcomes under alternative treatments, and uncertainty. Clinicians could then examine why the model favors one strategy over another and determine whether the computational recommendation is consistent with clinical judgment.

Such an architecture would allow the digital twin to function as a living computational model of the patient. However, its reliability would de-

pend on high-quality data, appropriate model selection, robust validation, and continuous monitoring of performance.

Digital Twins In Early-Stage Breast Cancer

Early-stage breast cancer may represent one of the most important settings for digital twin applications because treatment decisions frequently involve balancing the benefits of reducing recurrence risk against treatment-related toxicity. Many patients receive multimodal treatment, yet the magnitude of benefit from each intervention can differ substantially between individuals.

A digital twin could be established at diagnosis using clinical characteristics, imaging, pathology, receptor status, molecular information, and patient preferences. It could then estimate the patient's baseline recurrence risk and simulate potential treatment pathways. Rather than simply classifying the patient into a broad risk category, the system could potentially estimate how the expected outcome changes when specific treatment components are added or removed.

Neoadjuvant treatment provides a particularly valuable opportunity for digital twin development. Patients receiving systemic therapy before surgery can be monitored through repeated im-

aging, clinical assessment, and, in some settings, molecular biomarkers. The digital twin could use these sequential observations to estimate treatment sensitivity. If the tumor responds rapidly, the model could update its prediction of pathological response. If response is limited, the model could identify a higher probability of residual disease and potentially support consideration of alternative strategies.

Pathological complete response is clinically important in several breast cancer subtypes. A digital twin could integrate pretreatment characteristics with the observed response trajectory to estimate the probability of complete response before surgery. This could potentially help guide future adaptive treatment approaches, although clinical implementation would require prospective validation.

Surgical planning could also benefit from computational modeling. A digital twin could integrate imaging-defined tumor extent with pathological and biological information to support individualized planning. In selected cases, computational simulations could help compare breast-conserving approaches with more extensive surgery while considering tumor distribution and predicted residual disease.

Radiotherapy represents another potential application. A digital twin could integrate surgical findings, tumor biology, anatomical information, and radiation dose distribution. Alternative radiation plans could then be compared according to predicted tumor control and normal-tissue exposure. The system could potentially incorporate individual factors associated with treatment toxicity and long-term quality of life.

Adjuvant systemic treatment could be evaluated using a similar approach. The digital twin could combine clinical and molecular characteristics with previous treatment response and patient-specific risk factors. It could estimate the expected absolute benefit of chemotherapy, endocrine therapy, HER2-directed therapy, or other interventions while also considering toxicity.

This approach could be particularly valuable when treatment decisions are uncertain. In some patients, the expected benefit of an additional therapy may be relatively small, while treatment burden may be substantial. A digital twin could help make this tradeoff explicit by presenting individualized estimates rather than relying exclusively on population averages.

However, digital twins should not be viewed as replacements for validated clinical tools or established evidence. Their primary role would be to integrate information and provide individualized predictions that complement existing evidence. Prospective trials would be required to determine whether digital twin-guided decisions improve outcomes compared with conventional

multidisciplinary care.

Digital Twins In Metastatic And Recurrent Breast Cancer

Metastatic breast cancer presents a particularly strong rationale for digital twin technology because disease biology may change repeatedly during treatment. Metastatic tumors can develop resistance to endocrine therapy, HER2-directed therapy, chemotherapy, targeted therapy, or immunotherapy. Different metastatic sites may also display distinct biological characteristics. Consequently, treatment decisions require continuous reassessment rather than a single definitive treatment plan.

A metastatic breast cancer digital twin could integrate the original tumor characteristics with data obtained from metastatic lesions, liquid biopsy, imaging, treatment history, and clinical outcomes. This would allow the computational model to distinguish the current disease state from characteristics recorded at initial diagnosis.

One important application would be treatment sequencing. A patient may have several potential systemic treatment options, and the optimal sequence may depend on previous therapy, response duration, molecular changes, organ involvement, and toxicity. A digital twin could simulate alternative treatment sequences and

estimate their potential effects on disease control and adverse outcomes.

Longitudinal circulating tumor DNA could provide an important source of information. Changes in circulating tumor DNA may provide molecular evidence of treatment response or emerging resistance before radiographic progression becomes apparent in some circumstances. If validated for a particular clinical application, such data could be incorporated into the digital twin to update estimates of disease activity.

Imaging would provide complementary information. PET, CT, MRI, and other imaging modalities can describe the distribution and size of metastatic disease. A digital twin could analyze changes over time and potentially distinguish different patterns of response across metastatic sites. This may be especially relevant when some lesions respond while others progress.

The digital twin could also help model treatment toxicity. Patients with metastatic disease may receive multiple lines of therapy over extended periods. Cumulative toxicity can affect treatment choices, particularly when therapies influence cardiac, hepatic, renal, neurological, or hematological function. A patient-specific model could integrate previous toxicities with current clinical characteristics to estimate the expected burden of alternative treatment strategies.

Quality of life should be central to these models. In metastatic breast cancer, treatment goals may involve prolonging survival while maintaining functional status and minimizing symptoms. A digital twin could potentially incorporate patient-reported outcomes and preferences into treatment simulations. This could support shared decision-making in situations where several treatments have similar expected disease-control outcomes but different effects on quality of life.

Another potential application is early identification of treatment resistance. A digital twin could analyze multiple longitudinal signals, including imaging, molecular biomarkers, symptoms, and laboratory data. A divergence between expected and observed response could trigger additional clinical assessment.

The future of metastatic breast cancer management may therefore involve continuously updating computational representations that evolve with the disease. Such systems could support individualized treatment sequencing rather than assuming that a predefined sequence is optimal for every patient.

Artificial Intelligence, Multi-Omics, And Treatment Simulation

Artificial intelligence is likely to provide a major technological foundation for breast cancer digital twins. Breast cancer generates diverse and high-dimensional data through imaging, pathology, molecular testing, clinical records, and longitudinal monitoring. AI can analyze these data individually and jointly, potentially revealing relationships that are difficult to identify through conventional statistical approaches.

Medical imaging is one of the most developed areas. Deep learning models can assist with breast lesion detection, classification, segmentation, and risk estimation. Within a digital twin, imaging models could generate quantitative representations of tumor phenotype and treatment response. Serial images could then be analyzed as a trajectory rather than as isolated examinations.

Digital pathology provides another opportunity. Whole-slide images contain enormous amounts of information about cellular morphology, tissue architecture, stromal characteristics, immune infiltration, and tumor heterogeneity. AI could extract features from these images and integrate them with molecular and clinical data. Multi-omics integration could provide deeper biological characterization. Genomics, transcriptomics, proteomics, metabolomics, and epigenomic data can describe different layers of tumor biology. A digital twin could combine these data to identify biological pathways associated with treatment response or resistance. Natural

language processing could extract information from clinical notes, pathology reports, imaging reports, and treatment records. This would reduce the amount of clinically relevant information that remains inaccessible because it is stored in unstructured text.

Treatment simulation would be the next step. Once the digital twin contains a sufficiently detailed representation of the patient's disease, computational models could estimate how the disease might respond to different interventions. For example, the system could compare treatment strategies according to predicted recurrence risk, tumor response, toxicity, and quality of life. Mechanistic modeling could complement AI. A machine learning model may recognize that certain molecular and imaging patterns are associated with treatment response, but it may not explain the biological mechanism. Mechanistic models can represent processes such as tumor growth, drug exposure, cell death, and resistance development. A hybrid model could therefore combine the predictive capacity of AI with biological constraints.

Reinforcement learning may eventually be investigated for sequential treatment optimization. Such approaches could model treatment as a series of decisions in which each intervention changes the future disease state. However, because errors in treatment recommendations can

have serious consequences, reinforcement learning systems would require extensive validation and strong safeguards before clinical deployment.

Explainability is essential throughout this process. Clinicians should be able to identify the principal variables contributing to a prediction. The system should also distinguish between direct clinical observations and model-derived conclusions. The combination of AI, multi-omics, imaging, and mechanistic modeling could therefore transform the digital twin into a comprehensive precision oncology platform. Its purpose would not be simply to predict outcomes but to simulate possible futures and help clinicians choose among them.

Adaptive Treatment And Personalized Clinical Decision-Making

Digital twins could support a shift from fixed treatment pathways toward adaptive treatment strategies. In conventional oncology, treatment is often planned using information obtained at diagnosis and modified when substantial evidence of progression or toxicity appears. A digital twin could potentially provide a more continuous approach by incorporating smaller changes in disease state as they occur.

For patients receiving neoadjuvant therapy, repeated imaging and clinical assessments could

update the digital twin throughout treatment. The model could estimate whether the observed trajectory is consistent with effective therapy. If response is substantially different from expectations, clinicians could reassess the treatment strategy. In the adjuvant setting, the digital twin could estimate long-term recurrence risk while incorporating emerging information. This could potentially support more individualized decisions regarding treatment intensity and duration. However, any such application would require evidence demonstrating that computational recommendations improve outcomes without increasing recurrence risk.

In metastatic disease, adaptive treatment may be even more relevant. The digital twin could monitor disease trajectory and identify discrepancies between predicted and observed outcomes. When emerging resistance is suspected, alternative treatments could be computationally compared before clinical progression becomes extensive. Treatment toxicity could also be incorporated into adaptive decision-making. A patient's tolerance of therapy is dynamic. Renal function, cardiac function, hematological parameters, symptoms, and quality of life can change during treatment. A digital twin could incorporate these variables into treatment simulations, helping clinicians evaluate the balance between efficacy and tolerability.

Patient preferences should be incorporated explicitly. Some patients may prioritize maximum reduction in recurrence risk, while others may place greater value on avoiding chemotherapy or preserving quality of life. The digital twin could potentially generate different scenarios according to patient-defined priorities. Shared decision-making could therefore become more quantitative without becoming less human. The physician would remain responsible for interpreting the evidence, discussing uncertainty, and understanding patient preferences. The digital twin would provide additional computational information to support that process.

An important requirement would be transparent communication. Predictions should be presented as probabilities rather than certainties. Clinicians and patients should understand that the model may be wrong, particularly when the patient's characteristics differ from those represented in the training data.

The ultimate goal would be a closed-loop system in which data are collected, analyzed, modeled, and used to inform treatment, followed by further data collection and model updating. Such a cycle could make breast cancer management increasingly responsive to the patient's changing disease state.

High Accuracy Of Treatment

Prediction In Breast Cancer By Digital Twins

Breast cancer is the most commonly diagnosed cancer among women, and early diagnosis plays a critical role in the treatment process due to the heterogeneous nature of breast cancer. Current therapeutics struggle to address patient differences and complexity. Predicting a patient's response to medication in breast cancer is one prominent application of this technology. Neoadjuvant therapy (NAT) is currently one of the main standards of care among triple-negative breast cancer (TNBC) patients, which leads to a decrease in tumor burden prior to surgery and elevates the opportunity to overcome disease and metastasis; however, approximately more than 50% of TNBC patients who receive NAT never exhibit a complete response to medications prior to surgery due to the high levels of heterogeneity in tumor cells and patients, which is one major limitation of this method. One therapeutic answer to this heterogeneous nature is combining several methods or medications, such as immunotherapy medications like pembrolizumab with chemotherapy, which has exhibited a great deal of success in pCR; however, this leads to elevated levels of toxicity for the patient. Therefore, a personalized medication regimen derived by digital twins may substantially alter the outcome of therapies and decrease the tumor burden before surgery by identifying the

best medication or medication dosage for each patient, and this approach elevates the quality of life in patients. Moreover, DT technology is a relatively less expensive method compared with conventional clinical trials, which are resource-intensive and incapable of investigating all therapeutics in a comprehensive study. Mathematical models have also previously exhibited considerable achievement in accurately predicting responses to therapeutics. Jarret et al., in their investigation of a cohort of 18 invasive breast cancer patients, illustrated that by integrating magnetic resonance imaging (MRI) data into a biophysical model of the patient's particular characteristics, including tumor progression and the physical type of breast tissue, the result would be a predictive mathematical model totally capable of predicting tumor response to therapeutics. Also, Wu et al., in their developed predictive framework for predicting the outcome of neoadjuvant chemotherapies on TNBC, have shown the ability of digital twins to predict the outcome of a particular treatment. In this study, they used MRI data to construct the digital twins, and patients who received personalized digital twin-optimized medications exhibited substantial improvement in pathological complete response (pCR). The application of digital twins in breast cancer particularly increases in importance in older breast cancer patients due to the fact that older patients are often underrepresented in in-

vestigations. Heudel et al., using a retrospective analysis of a HER2-negative female breast cancer cohort over the age of 70, developed a model to predict treatment outcomes of medications that is capable of stratifying patients into subgroups based on their biology and suitable therapeutics with an accuracy of 81% and also represents a risk of death among patients with multivariate profiles within 5 years. In a 2023 study by Konopik et al., a qualitative analysis carried out on the interview results of a group of breast cancer patients who were undergoing treatment illustrated the great potential for a positive role of DT technology in personalized medicine. In another study by Meraghni et al., scanning breast surface heat was introduced as a non-invasive method for suggesting a DT model for breast cancer diagnosis. According to this study, current breast cancer screening techniques have limitations, including long procedures and high expenses; therefore, thermography, or radiation-free recording of the temperature of the breast, emerged as a fast method for the early diagnosis of breast cancer masses. However, as thermographic data might not be highly accurate, in this study, the patient's biothermal data were overlapped with DT to be amalgamated with multiple other data sources acquired from smart devices, and through real-time analysis of the patient's data, the DT could help with diagnosis.

Digital Twins In Precisely Locating Breast Tumors

In addition to predicting drug response and optimizing therapeutic prediction in breast cancer, the DT could also be a helpful tool for tumor localization. While current methods for tumor localization in breast cancer surgery are invasive, Timoteo et al. developed a DT model for breast cancer tumor localization based on digitally segmented breast tissue from MRI scans. Breast cancer surgery and tumor localization during surgery rely on MRI; therefore, the DT models are then aligned with real-time tumor surface scans to project the tumor coordinates and suggest a non-invasive tumor localization method that guides the surgeon through the surgery. Also, this study showed that the surgeons reported a less intensive workload and satisfactory alignment between the DT-localized tumors and true tumor localization. Current breast cancer digital twin models primarily rely on imaging and tumor growth dynamics, while the integration of transcriptomic drug-resistance signatures has remained underexplored; therefore, this opens a door to future investigations in this area.

Challenges, Ethical Considerations, And Clinical Validation

The development of breast cancer digital twins faces several major challenges. Data integra-

tion is one of the most immediate. Imaging, pathology, genomics, clinical records, and patient-reported outcomes are often stored in different systems. Standardized data structures and interoperability will be necessary to combine them effectively.

Data quality is equally important. Missing information, inconsistent imaging protocols, differences in pathology interpretation, and variations in molecular testing can reduce model performance. Digital twins require mechanisms for identifying unreliable data and communicating uncertainty when information is incomplete.

Breast cancer heterogeneity presents another fundamental challenge. Tumors can contain multiple cellular populations, and different metastatic sites may have different molecular characteristics. A single biopsy or imaging examination may therefore provide an incomplete representation of the disease.

Temporal evolution adds additional complexity. Treatment can change the biological composition of the tumor. A digital twin must therefore be continuously updated rather than permanently anchored to the initial diagnosis.

Privacy is a major concern because these systems may integrate genomic information, detailed clinical histories, imaging, and long-term

outcomes. Strong cybersecurity and governance mechanisms will be required to protect patients.

Algorithmic bias is another potential problem. If datasets predominantly represent patients from particular geographic, ethnic, socioeconomic, or healthcare settings, the resulting models may not perform equally well across populations. External validation and fairness assessment should therefore be integrated into development.

Automation bias must also be considered. Clinicians may place excessive confidence in computational recommendations, especially when systems appear highly sophisticated. Digital twins should therefore provide explanations and uncertainty estimates and should be used within appropriate clinical oversight.

Clinical validation is essential. Retrospective accuracy alone is insufficient. Prospective studies should determine whether digital twin-guided treatment improves outcomes such as recurrence, survival, treatment toxicity, quality of life, and patient satisfaction.

Regulatory oversight will also be necessary as digital twins begin influencing treatment decisions. Models that continuously learn may create additional challenges because their behavior can change over time. Monitoring frameworks should therefore assess performance after deployment and identify when recalibration or re-

training is necessary.

Another important consideration is cost and accessibility. Advanced digital twin systems could initially require substantial computational infrastructure, specialized personnel, and access to extensive molecular testing. If implementation is limited to highly specialized centers, technological advances could inadvertently increase disparities in cancer care.

Future research should therefore prioritize scalable architectures and clinically meaningful endpoints. The most successful digital twins will not necessarily be the most technically complex systems. They will be the systems that reliably improve decisions, integrate naturally into clinical workflows, and provide measurable benefits to patients.

Future Perspectives And Conclusion

Digital twins have the potential to become an important component of next-generation breast cancer treatment by creating dynamic computational representations that integrate the biological and clinical characteristics of individual patients. Their greatest potential lies in their ability to move beyond static risk prediction and support continuous modeling of disease evolution, treatment response, resistance, toxicity, and patient outcomes.

For early-stage breast cancer, digital twins could help personalize treatment intensity, evaluate neoadjuvant response, support surgical and radiotherapy planning, and estimate the potential benefit of systemic therapies. For metastatic disease, they could support treatment sequencing, resistance monitoring, toxicity management, and quality-of-life optimization.

The integration of artificial intelligence, advanced imaging, digital pathology, multi-omics, circulating biomarkers, and mechanistic modeling could make these systems increasingly sophisticated. Instead of analyzing each data type separately, future digital twins may construct a unified representation of the tumor and the patient. This representation could be updated continuously as new evidence emerges.

One of the most important future developments could be treatment simulation. Clinicians may eventually be able to compare several treatment pathways using a patient-specific computational model before selecting a strategy. The model could estimate expected disease control, recurrence, toxicity, and quality of life while explicitly representing uncertainty.

However, digital twins should not be regarded as autonomous replacements for clinical expertise. Their predictions will always depend on the quality of their data, assumptions, and models. Rigorous prospective validation will therefore

be essential. Future research should determine whether these technologies improve clinical outcomes rather than simply demonstrating technical predictive performance.

Ethical and regulatory considerations will be equally important. Patient privacy, cybersecurity, algorithmic fairness, explainability, informed consent, accountability, and equitable access must be addressed from the beginning of development. Continuous monitoring will be necessary because both cancer biology and clinical practice evolve over time.

The most realistic future is therefore not one in which digital twins independently decide how breast cancer should be treated. Instead, they may become sophisticated computational partners for multidisciplinary oncology teams. They could organize complex information, identify clinically meaningful patterns, simulate treatment scenarios, quantify uncertainty, and help clinicians and patients understand the consequences of different choices.

If validated and implemented responsibly, digital twins could contribute to a fundamental transformation in breast oncology. Treatment could increasingly be based not only on what the tumor looked like at diagnosis, but also on how it has evolved, how it has responded to previous interventions, how the patient's biological condition has changed, and what outcomes matter

most to the individual. Such an approach could help transform precision medicine from a primarily diagnostic concept into a dynamic therapeutic framework in which treatment continuously adapts to the evolving biology and needs of each patient.

5. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN LUNG CANCERS

Background

Next-generation cancer treatment is increasingly shaped by the convergence of advanced computational modeling, precision medicine, and real-time patient data integration. Among emerging innovations, the concept of "digital twins" has gained significant attention as a transformative approach in oncology, particularly in the management of complex and heterogeneous diseases such as lung cancer. A digital twin can be defined as a dynamic, virtual representation of a patient that continuously integrates clinical, biological, and environmental data to simulate disease progression and predict responses to therapeutic interventions. This paradigm shift moves oncology beyond static, population-based treatment strategies toward highly individualized and adaptive care models.

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, largely due to late-stage diagnosis, tumor heterogeneity, and variable responses to treatment. Despite advances in targeted therapies and immunotherapy, clinical decision-making often relies on limited snapshots of patient data, such as im-

aging or biopsy results, which may not fully capture the dynamic evolution of the disease. In this context, digital twin technology offers a promising solution by enabling continuous monitoring and predictive modeling of tumor behavior. By integrating multimodal data, including radiological imaging, genomic profiling, histopathological features, and treatment history, digital twins can provide a comprehensive and evolving representation of each patient's disease.

The application of digital twins in lung cancer has the potential to revolutionize several aspects of clinical care. First, it enables personalized treatment planning by simulating the effects of different therapeutic strategies before they are administered in reality. For instance, a patient-specific digital model could be used to predict the efficacy of immunotherapy versus targeted therapy based on the tumor's molecular profile and microenvironment. Second, digital twins can facilitate the early detection of treatment resistance or disease progression by identifying subtle changes in tumor dynamics that may not yet be clinically apparent. This proactive approach allows clinicians to adjust treatment regimens in a timely manner, potentially improving patient outcomes.

Moreover, the integration of artificial intelligence and machine learning algorithms enhances the predictive power of digital twins.

These technologies can analyze vast amounts of longitudinal data to identify patterns and correlations that are not discernible through traditional methods. As a result, digital twins can evolve alongside the patient, continuously refining their predictions and recommendations based on newly acquired data. This iterative process reflects a shift toward a learning healthcare system, in which each patient contributes to the improvement of future care.

Despite its promise, the implementation of digital twin technology in lung cancer faces several challenges. Data standardization, interoperability between healthcare systems, and concerns regarding patient privacy and data security remain significant barriers. Additionally, the clinical validation of digital twin models requires rigorous prospective studies to ensure their reliability and accuracy. Ethical considerations also arise regarding the extent to which clinicians should rely on algorithm-driven recommendations in critical decision-making processes.

In conclusion, digital twins represent a compelling frontier in the evolution of precision oncology, particularly for complex diseases such as lung cancer. By bridging the gap between biological complexity and computational intelligence, this approach holds the potential to transform cancer care into a more predictive, preventive, and personalized discipline. Con-

tinued interdisciplinary collaboration among clinicians, data scientists, and engineers will be essential to translate this innovative concept from theoretical promise into routine clinical practice.

Digital twins (DTs) are versatile technologies that support and facilitate predictive simulations in several industries. In the area of healthcare, digital twins, as replicas of human bodies that develop over time with new data, integrate radiological, physiological, and bioinformatic information with artificial intelligence technology to model diseases and provide opportunities for personalized medicine, disease prediction, prediction of disease recurrence, treatment optimization, and treatment cost reduction. Advances in healthcare-related technologies, including omics, along with progressive growth in clinical research and scientific analyses based on public health records, have resulted in the emergence of a “cancer big data” concept, which has led to a growing need for precise data management, clustering, analysis, and extraction of meaningful results through the development of artificial intelligence (AI) frameworks. Digital twins have multiple applications in cancer research, including integrating mutations, molecular pathways, RNA-seq, and previous patient responses to medications in order to obtain a simulation of tumors and

their responses to therapeutics. DTs collect data from multiple sources of information and integrate them to achieve a digital replica of the patient with the aim of refining clinical decision-making, which benefits the real patient. These integrated datasets can provide a more comprehensive representation of disease characteristics and patient-specific responses, while supporting the identification of clinically meaningful patterns that may otherwise remain difficult to recognize through conventional analytical approaches alone, improving the interpretation of complex clinical information for more informed decisions.

Digital Twin Architecture For Lung Cancer

A clinically useful lung cancer digital twin would require an architecture capable of integrating multiple data streams and updating the computational representation as the patient's disease changes. The physical patient would remain the biological system being treated, while the digital twin would provide a virtual representation that reflects the available clinical evidence. Several interconnected components would be required, including data acquisition, multimodal integration, computational modeling, synchronization, prediction, visualization, and clinical decision support.

Thoracic imaging would constitute one of the most important components. Computed tomography provides detailed information about primary tumors, pulmonary nodules, lymph nodes, pleural involvement, and metastatic disease. Positron emission tomography can provide complementary information regarding metabolic activity and disease distribution. Serial imaging can reveal changes in tumor size, density, morphology, and metabolic characteristics during treatment. Artificial intelligence could segment tumors and metastatic lesions and extract quantitative radiomic characteristics that may provide information beyond conventional visual interpretation.

Pathology would provide another major component. Histological classification, tumor differentiation, molecular characteristics, and pathological response can substantially influence treatment decisions. Digital pathology could allow computational analysis of tissue architecture, cellular morphology, immune infiltration, stromal characteristics, and other features. When integrated with imaging, pathology could provide complementary information about the biological state of the tumor.

Molecular information would further increase the resolution of the digital twin. Genomic profiling could identify actionable alterations and resistance-associated changes. Transcriptomic

and proteomic information could potentially describe biological pathways involved in tumor growth and treatment response. Circulating tumor DNA could provide repeated molecular observations without requiring repeated tissue biopsies. These longitudinal molecular measurements could allow the digital twin to detect changes in disease biology over time.

Clinical information should also be integrated. Age, smoking history, pulmonary function, performance status, comorbidities, previous treatments, medication use, laboratory values, and patient-reported symptoms can influence both treatment eligibility and outcomes. Pulmonary reserve is particularly important in lung cancer because treatment may affect respiratory function, while pre-existing cardiopulmonary disease may substantially alter treatment tolerance.

The computational layer could contain several specialized models. Machine learning algorithms could estimate response or progression risk. Deep learning models could analyze imaging and pathology. Pharmacokinetic and pharmacodynamic models could estimate drug exposure and effects. Mechanistic tumor-growth models could represent spatial progression. Probabilistic models could quantify uncertainty when data are incomplete or contradictory.

Synchronization would allow the digital twin to evolve with the patient. New imaging could

modify estimates of tumor burden. A new biopsy could change the molecular profile. Detection of a resistance-associated alteration could modify treatment predictions. A change in pulmonary function could alter the expected toxicity of an intervention. Thus, the digital twin would not be a one-time computational product but a continuously updated representation.

An effective interface would be essential. Clinicians should be able to review the current disease state, examine longitudinal changes, compare treatment scenarios, and identify the factors responsible for computational predictions. The system should distinguish clearly between observed clinical evidence and model-derived estimates. Predictions should also include uncertainty rather than presenting computational outputs as definitive conclusions.

Such an architecture could provide a foundation for individualized lung cancer management. However, its clinical value would ultimately depend on the quality of the underlying data, the validity of the computational models, interoperability between healthcare systems, and prospective evidence demonstrating improved patient outcomes.

Digital Twins In Early-Stage And Locally Advanced Lung Cancer

Early-stage and locally advanced lung cancer represent important settings for digital twin applications because treatment decisions frequently require integration of imaging, pathology, anatomical information, pulmonary function, and patient-specific risk factors. Surgery, radiotherapy, systemic therapy, or combinations of these approaches may be appropriate depending on tumor characteristics and patient fitness. Digital twins could potentially help personalize these decisions by simulating treatment outcomes for individual patients.

At diagnosis, the digital twin could integrate computed tomography, positron emission tomography, biopsy findings, molecular information, pulmonary function, performance status, and comorbidities. It could then generate a baseline representation of the tumor and the patient's ability to tolerate treatment. Rather than focusing only on tumor stage, the model could consider multiple interacting factors when estimating future outcomes.

Surgical planning represents a potential application. A digital twin could incorporate tumor location, anatomical relationships, pulmonary reserve, and other clinical characteristics to simulate different surgical strategies. For patients with limited respiratory function, the model could estimate the potential consequences of different degrees of lung resection on postoperative function. Such simulations would

not replace thoracic surgical judgment but could provide additional quantitative information for multidisciplinary decision-making.

Radiotherapy planning could also benefit from digital twin technology. The computational model could integrate tumor location, target volume, surrounding structures, and planned radiation dose. Alternative treatment plans could be compared according to predicted tumor control and normal-tissue exposure. For selected patients receiving stereotactic approaches, the digital twin could potentially incorporate tumor characteristics and anatomical information to support individualized treatment planning.

Neoadjuvant and perioperative systemic therapies provide another opportunity. Patients receiving treatment before surgery can be monitored through repeated imaging and, increasingly, molecular measurements. A digital twin could use the observed treatment trajectory to estimate response and potential pathological outcomes. If the observed response differs substantially from the predicted trajectory, clinicians could reassess the treatment strategy.

The integration of circulating tumor DNA could be particularly valuable in this setting. Molecular changes detected during or after treatment may provide information about residual disease or recurrence risk. A digital twin could incorporate these measurements alongside imaging and

pathological findings to generate a more comprehensive estimate of disease status.

Postoperative management could also become more individualized. The digital twin could combine surgical pathology, molecular characteristics, residual disease indicators, and patient-specific factors to estimate recurrence risk and evaluate potential benefits of adjuvant therapy. Such a framework could help distinguish patients likely to derive substantial benefit from additional treatment from those for whom treatment burden may outweigh the expected benefit.

Longitudinal surveillance represents another potential application. Instead of interpreting each follow-up scan independently, the digital twin could analyze the patient's entire imaging trajectory. Small changes that might be difficult to interpret in isolation could be assessed within the context of previous imaging, treatment history, and molecular measurements.

However, prospective evidence would be required before such systems could influence treatment decisions. Early-stage lung cancer involves potentially curative interventions, so computational errors could have substantial consequences. Digital twins should therefore complement established clinical evidence rather than replace validated staging systems, multidisciplinary assessment, or guideline-based care.

Digital Twins In Advanced And Metastatic Lung Cancer

Advanced and metastatic lung cancer may provide an especially strong use case for digital twins because treatment often involves multiple sequential interventions and disease biology can change substantially over time. Patients with metastatic non-small cell lung cancer may receive targeted therapy, immunotherapy, chemotherapy, antibody-based approaches, or combinations of these strategies. Small cell lung cancer may also require sequential systemic treatment and careful monitoring of treatment response and progression. The optimal treatment pathway can differ considerably between individuals.

A metastatic lung cancer digital twin could integrate the characteristics of the primary tumor, metastatic sites, molecular profile, previous treatment exposure, imaging, circulating biomarkers, symptoms, and organ function. At each clinically relevant time point, the system could update its representation of disease state and estimate potential future trajectories.

Treatment sequencing could be a central application. A patient may have several potential therapeutic options, and the optimal sequence may depend on previous response, resistance mechanisms, toxicity, molecular characteristics, and disease distribution. A digital twin could simu-

late alternative sequences and compare their expected benefits and risks.

Acquired resistance is particularly important in molecularly targeted lung cancer. A tumor that initially responds to targeted therapy may later progress because of secondary molecular alterations or other biological mechanisms. Serial liquid biopsy could potentially identify emerging molecular changes. If incorporated into the digital twin, these data could modify the predicted probability of response to current or alternative treatments.

Heterogeneous progression presents another challenge. Different metastatic lesions may behave differently. Some lesions may respond while others continue growing. A single overall measurement may therefore fail to represent the complete disease state. A digital twin could potentially model disease at the lesion level and identify spatially distinct patterns of response and resistance.

Immunotherapy creates additional opportunities and challenges. Responses may be prolonged in some patients but absent in others. Biomarkers such as PD-L1 expression provide useful information but do not completely determine response. The digital twin could potentially combine immune biomarkers, tumor characteristics, imaging, treatment history, and longitudinal outcomes to estimate response more

comprehensively.

Treatment toxicity should also be incorporated. Patients with advanced lung cancer may have limited pulmonary reserve and substantial comorbidity. Therapies can produce hematological, cardiac, renal, neurological, gastrointestinal, or pulmonary toxicities. A patient-specific model could incorporate previous adverse events and current organ function when comparing treatment strategies.

Quality of life should remain a central outcome. In advanced disease, the value of a treatment cannot be measured solely by tumor response. Symptoms, respiratory function, mobility, fatigue, pain, treatment burden, and independence are also important. A digital twin could incorporate patient-reported outcomes and preferences into treatment simulations.

The digital twin could therefore support a continuous process of disease monitoring and treatment adaptation. Rather than waiting until conventional imaging demonstrates substantial progression, the system could integrate multiple signals and identify changes in the expected disease trajectory. Such predictions would require careful validation, but they illustrate how digital twins could potentially transform metastatic lung cancer management.

Artificial Intelligence, Radiomics,

And Multi-Omics Integration

Artificial intelligence will likely play a central role in the development of digital twins for lung cancer because the disease generates complex and multimodal datasets. Thoracic imaging, pathology, genomic sequencing, liquid biopsy, clinical records, laboratory measurements, and treatment histories each describe different aspects of the disease. AI can provide computational methods for integrating these sources and identifying relationships that may not be apparent when they are analyzed separately.

Radiomics represents one important component. Computed tomography contains quantitative information about tumor size, shape, texture, density, margins, internal architecture, and surrounding tissues. AI-based segmentation can identify primary tumors and metastatic lesions, while radiomic models can extract high-dimensional features. Serial radiomic measurements could then be used to characterize changes during treatment.

Deep learning could also contribute to automated detection and characterization of pulmonary lesions. Within a digital twin, these systems could provide structured information about tumor phenotype and its evolution. The objective would not simply be to detect a lesion but to integrate imaging characteristics with molecular and clinical information.

Digital pathology provides another major data source. AI can analyze whole-slide images to identify cellular morphology, tissue architecture, immune infiltration, and other features. These data could be combined with imaging and molecular information to create a more comprehensive representation of tumor biology.

Multi-omics integration could further improve the digital twin. Genomic alterations, gene expression, protein activity, metabolic pathways, and epigenetic changes can provide complementary information. A computational model could potentially identify molecular patterns associated with sensitivity or resistance to particular therapies.

Natural language processing could extract information from pathology reports, radiology reports, oncology notes, and treatment records. Important information that is currently stored in unstructured text could then be incorporated into the digital twin. This could reduce information loss and improve longitudinal modeling.

Mechanistic modeling could complement AI-based approaches. Data-driven models are capable of identifying complex associations, but their predictions may not always be biologically interpretable. Mechanistic models can represent tumor growth, drug exposure, radiation effects, and other biological processes. A hybrid system could use AI to estimate patient-specific parameters while maintaining biologically meaningful constraints.

Treatment simulation could then be performed using the integrated digital twin. Different treatment strategies could be modeled according to their predicted effects on tumor burden, resistance, toxicity, and quality of life. Such simulations could potentially be especially valuable when multiple therapeutic options are available.

Explainability would be essential. Clinicians should understand which factors are contributing to a prediction and how reliable the prediction is. A model that identifies a high probability of treatment resistance should ideally provide information about whether the prediction is driven by molecular findings, imaging trajectory, prior treatment response, or other variables.

Continuous learning could allow the digital twin to become increasingly individualized. Each new observation could update the patient's computational representation. However, continuous learning requires rigorous quality control to prevent erroneous observations from altering the model inappropriately.

The integration of AI, radiomics, pathology, multi-omics, and mechanistic modeling could ultimately transform the digital twin into a comprehensive computational platform for lung cancer. Its purpose would be to connect complex

biological information with practical clinical decisions.

Adaptive Treatment And Personalized Decision-Making

Digital twins could enable a transition from predefined treatment pathways toward adaptive therapeutic strategies. Conventional treatment plans are often established at diagnosis and modified when progression or significant toxicity becomes apparent. A digital twin could potentially provide more continuous assessment by integrating new information throughout treatment.

During neoadjuvant therapy, repeated imaging and molecular measurements could be used to estimate whether the tumor is following an expected response trajectory. If the response is substantially weaker than anticipated, the model could indicate that the probability of successful treatment has changed. Clinicians could then reassess the available options.

Following surgery, the digital twin could incorporate pathological findings, margin status, lymph node involvement, molecular characteristics, and postoperative information. It could then estimate recurrence risk and potential benefits from additional therapy. This could support more individualized postoperative treatment strategies.

During radiotherapy, a digital twin could potentially model the interaction between tumor response and radiation exposure. If anatomical changes occur during treatment, the model could help evaluate whether adaptation of the radiation plan might provide benefits. Such applications would require extensive technical and clinical validation.

In metastatic disease, adaptive treatment may be particularly valuable. The digital twin could continuously integrate imaging, circulating tumor DNA, symptoms, and treatment exposure. If evidence of resistance begins to emerge, alternative treatment strategies could be computationally compared.

Toxicity monitoring could also become more personalized. A patient with limited pulmonary function may face different risks from treatment than a patient with preserved respiratory capacity. Incorporating pulmonary function, comorbidities, previous adverse events, and current symptoms could help estimate the balance between treatment benefit and toxicity.

Patient preferences should be incorporated into decision-making. Some patients may prioritize maximum survival, whereas others may place greater emphasis on preserving respiratory function, avoiding hospitalization, or maintaining independence. The digital twin could present alternative treatment scenarios according

to different priorities.

Shared decision-making would remain essential. Digital twin outputs should be presented as estimates rather than certainties, and patients should be informed about the limitations of the models. The physician's clinical judgment remains necessary to interpret predictions in the context of the patient's overall circumstances.

The ideal system would create a continuous feedback loop. Data would be collected from the patient, analyzed by computational models, incorporated into the digital twin, and used to inform treatment decisions. The response to treatment would then generate new data, allowing the process to repeat.

This approach could eventually create a more responsive model of lung cancer care. Instead of relying primarily on predefined treatment sequences, clinicians could use a continuously updated computational representation to identify when the disease trajectory has changed and determine whether a different therapeutic strategy should be considered.

Challenges, Ethical Considerations, And Clinical Validation

Despite the potential benefits of digital twins, their implementation in lung cancer presents major scientific, technical, ethical, and clinical challenges. Data heterogeneity is one of the

most important. CT scanners, imaging protocols, laboratory systems, pathology methods, genomic platforms, and clinical documentation practices can differ substantially between institutions. Models trained in one environment may therefore perform poorly in another.

Data completeness is also important. Digital twins depend on longitudinal information, but clinical records often contain missing observations. Molecular testing may not be repeated at progression, imaging intervals may vary, and patient-reported outcomes may not be consistently collected. The model must therefore be capable of representing uncertainty rather than treating missing information as if it were normal information.

Tumor heterogeneity presents a biological challenge. Different regions of a lung tumor may contain different cellular populations, and metastatic lesions may evolve independently. A single biopsy may therefore provide only a partial representation of the disease. Future digital twins will need approaches that can integrate spatial and temporal heterogeneity.

Disease evolution creates another problem. A computational model created at diagnosis can become inaccurate after prolonged treatment. Continuous updating is essential, but the process introduces the risk of model drift. Changes in treatment standards, diagnostic technologies,

and patient populations can also affect model performance.

Privacy and cybersecurity require particular attention. A digital twin could contain highly sensitive clinical, genomic, imaging, and longitudinal information. Unauthorized access could expose not only current health information but also information about future disease risk. Strong encryption, access controls, governance frameworks, and appropriate consent procedures will therefore be essential.

Algorithmic bias is another concern. If training datasets do not adequately represent different populations, the digital twin may produce less accurate predictions for underrepresented groups. Multicenter validation and fairness assessment should therefore be incorporated into development.

Automation bias could also become a clinical risk. Clinicians may place excessive confidence in computational predictions, particularly when systems appear highly sophisticated. The digital twin should therefore communicate uncertainty, provide interpretable evidence, and remain within a framework of human clinical oversight.

Prospective clinical validation will be essential. A model demonstrating high accuracy in retrospective datasets does not necessarily im-

prove patient outcomes. Trials should evaluate whether digital twin-guided treatment improves survival, disease control, treatment toxicity, quality of life, and patient satisfaction.

Regulatory requirements will also become increasingly important. Systems that provide treatment recommendations may be considered medical technologies requiring evidence of safety and effectiveness. Continuous-learning systems may present additional regulatory challenges because their performance and behavior can change after deployment.

Cost and accessibility should also be considered. Advanced digital twins may initially require extensive computational infrastructure, molecular testing, high-quality imaging, and specialized expertise. If these technologies are available only in highly resourced centers, they could increase rather than reduce disparities.

Future development should therefore emphasize clinically useful systems that are scalable, interoperable, transparent, and evidence based. Technological complexity should not be considered an objective by itself. The most valuable digital twin will be the one that improves clinical decisions and meaningful outcomes for patients.

Future Perspectives And Conclusion

Digital twins have the potential to become an

important component of next-generation lung cancer treatment by providing dynamic computational representations of patients and their evolving disease. Their greatest potential lies in integrating multiple sources of information that are currently evaluated separately, including imaging, pathology, molecular profiling, circulating biomarkers, treatment history, physiological characteristics, and patient-reported outcomes.

In early-stage lung cancer, digital twins could support individualized surgical planning, radiotherapy optimization, neoadjuvant treatment monitoring, recurrence-risk assessment, and postoperative treatment selection. In advanced and metastatic disease, they could assist with treatment sequencing, resistance detection, toxicity management, and adaptive therapeutic strategies.

Artificial intelligence, radiomics, digital pathology, multi-omics, and mechanistic modeling could collectively provide the computational foundation for these systems. Rather than generating a single static prediction, future digital twins may simulate multiple possible disease trajectories under different treatment strategies. This could allow clinicians to compare therapeutic options according to expected tumor control, resistance, toxicity, pulmonary function, and quality of life.

One of the most important developments may

be the integration of longitudinal molecular and imaging information. A tumor that appears stable according to conventional imaging may demonstrate molecular changes suggesting emerging resistance, while imaging abnormalities may sometimes reflect treatment-related changes rather than active progression. By integrating these different signals, a digital twin could potentially provide a more nuanced representation of disease state.

Nevertheless, digital twins should not be considered replacements for clinical expertise or established evidence. Their predictions will depend on the quality of the data and models used to construct them. Rigorous prospective validation, external testing, continuous monitoring, and transparent reporting will therefore be necessary before widespread clinical implementation.

Ethical considerations must develop alongside technological innovation. Patient privacy, cybersecurity, algorithmic fairness, explainability, informed consent, accountability, and equitable access should be incorporated into digital twin development from the beginning. Continuous-learning systems will also require mechanisms to detect model drift and maintain clinical reliability.

The future of lung cancer treatment may ultimately involve a continuous interaction be-

tween the patient, clinical team, and computational model. The digital twin could organize complex information, monitor disease evolution, simulate alternative treatment strategies, and identify changes that warrant clinical reassessment. The physician would remain responsible for interpreting these predictions and incorporating them into shared decisions with the patient.

If developed and validated responsibly, digital twins could help transform lung cancer precision medicine from a predominantly static process into a dynamic therapeutic framework. Instead of asking only which treatment is generally effective for a particular cancer subtype, clinicians could increasingly ask which treatment strategy is most likely to provide the best balance of tumor control, resistance prevention, treatment safety, respiratory function, and quality of life for a particular patient at a particular stage of disease.

Such an approach could represent an important step toward next-generation oncology, in which treatment is continuously informed by the evolving biological state of the tumor and the changing clinical needs of the individual patient.

6. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN GASTROINTESTINAL CANCERS

Background

When someone receives a diagnosis of gastrointestinal cancer, whether it's in the stomach, pancreas, colon, liver, or esophagus, the news hits like a thunderbolt. These diseases don't just affect organs; they disrupt entire lives, families, and futures. GI cancers are among the toughest to treat. They're often diagnosed late, behave unpredictably, and respond differently from one patient to the next. Traditional treatments like surgery, chemotherapy, radiation, and newer immunotherapies help many, but too often they come with heavy side effects and uncertain results. What if we could test treatments on a perfect virtual copy of a patient's own cancer before touching a single real cell? That's the promise of digital twins, and it's beginning to change everything.

A digital twin is essentially a living, breathing virtual replica of a patient's body, tumor, or even their entire disease journey. It's built from a rich mix of real-world data: genetic profiles, detailed scans, blood tests, medical history, lifestyle habits, and even information about the gut microbiome that plays such a big role in digestive

cancers. Powered by advanced artificial intelligence and powerful computing, this digital version doesn't sit still. It learns and updates as the patient does, allowing doctors to run countless "what if" scenarios safely in the computer.

Imagine a woman with pancreatic cancer, one of the most feared GI malignancies. Instead of relying solely on standard protocols that work for some but not others, her care team creates a digital twin. They can simulate how her specific tumor might respond to a new combination of chemotherapy and immunotherapy. Will it shrink the mass enough for surgery? How will her unique immune system react? Could adjusting the radiation dose protect her healthy tissues while still hitting the cancer hard? These questions, which once took months of trial and error with real human costs, can now be explored virtually in days or weeks.

In colorectal cancer, digital twins are helping predict whether a patient will benefit from targeted therapies or new personalized vaccines. For stomach and esophageal cancers, they assist surgeons in planning complex operations and forecast how the body might handle recovery. The technology shines especially in complex cases where the tumor's environment, shaped by inflammation, bacteria in the gut, and individual genetics, makes standard predictions unreliable.

What makes digital twins feel truly hopeful is

their human focus. They acknowledge that every patient is unique. No two cancers are exactly alike, even if they carry the same name. By continuously feeding real patient data back into the model, doctors gain a dynamic tool that evolves with the disease, supporting truly personalized decisions rather than one-size-fits-all approaches.

Of course, this technology isn't perfect yet. Challenges around data privacy, validating the models in real clinical settings, high computing needs, and ensuring doctors and patients trust the recommendations remain. But progress is happening quickly. Research initiatives worldwide are testing digital twins in trials, and early results are encouraging, helping match patients to the right treatments faster, reducing unnecessary toxicity, and giving people more precious time.

As we stand on the edge of this new era, digital twins represent more than cutting-edge tech. They embody a shift toward care that truly sees the person behind the cancer. For patients and families facing GI cancer, this could mean fewer surprises, better outcomes, and renewed hope. The road ahead is full of possibility, and the fight against these devastating diseases may soon look very different, more precise, more compassionate, and ultimately more successful.

Digital twin technology has emerged as a promising approach to advance precision oncology in GI cancers. Rather than functioning as a static predictive model, a digital twin represents a dynamic virtual counterpart of an individual patient that continuously integrates clinical, radiological, pathological, and multi-omics data to simulate disease behavior and treatment response. Collectively, recent studies suggest that this technology may shift cancer management from standardized treatment algorithms toward patient-specific therapeutic decision-making.

Across GI malignancies, including colorectal, pancreatic, gastric, hepatocellular, and esophageal cancers, digital twins are being developed to support treatment selection, predict therapeutic response, estimate recurrence risk, and optimize longitudinal disease monitoring. The integration of AI with radiomics, genomics, transcriptomics, and other molecular data enables these models to capture the biological complexity of tumors more comprehensively than conventional clinical prediction tools. As a result, digital twins have the potential to identify the most effective therapeutic strategy while minimizing unnecessary toxicity and ineffective treatments.

The current literature also highlights the broader role of digital twins beyond individualized care. Their ability to perform in silico simulations may improve patient stratification, facilitate virtual clinical trials, and accelerate the

development and evaluation of novel targeted therapies and immunotherapies. These capabilities are particularly relevant for GI cancers, where substantial interpatient heterogeneity remains a major obstacle to treatment optimization.

Despite these advances, recent reviews consistently emphasize that digital twin technology remains at an early stage of clinical translation. Major challenges include the need for standardized longitudinal datasets, seamless integration of multimodal data, robust external validation, and solutions to regulatory and ethical concerns. Therefore, while digital twins are unlikely to replace clinical judgment in the near future, they are expected to become an important decision-support tool. The convergence of artificial intelligence, computational modeling, and precision medicine is likely to establish digital twins as a cornerstone of next-generation management for gastrointestinal cancers.

Digital Twin Architecture For Gastrointestinal Cancer Care

The development of a digital twin for gastrointestinal cancer requires a multidimensional architecture capable of representing the complexity of both the patient and the disease. The first component is a comprehensive patient data layer that collects information from multiple

clinical sources. Demographic characteristics, comorbidities, previous cancer history, medication use, performance status, nutritional parameters, laboratory findings, and symptoms can provide essential information about the patient's baseline condition. These data become particularly important when treatment tolerance and competing health risks influence therapeutic decisions.

The second component consists of diagnostic and imaging information. Gastrointestinal cancers are evaluated using multiple imaging modalities, including computed tomography, magnetic resonance imaging, positron emission tomography, ultrasound, endoscopic ultrasound, and specialized imaging techniques. Endoscopy provides direct visualization of mucosal abnormalities and enables tissue acquisition, while imaging contributes information about tumor size, anatomical invasion, lymph-node involvement, vascular relationships, and distant metastases. A digital twin can combine these observations to create a more comprehensive representation of tumor anatomy and disease extent.

Histopathology and molecular information form another critical layer. Tumor grade, histological subtype, differentiation, vascular invasion, lymphovascular invasion, and other pathological features influence prognosis and treat-

ment selection. Molecular profiling can provide information about mutations, gene expression, epigenetic changes, microsatellite instability, mismatch repair status, tumor mutational burden, and other biomarkers. In selected gastrointestinal cancers, molecular characteristics already guide targeted therapy or immunotherapy. Integrating these data into a digital twin could improve the ability to predict which treatments are most likely to benefit a specific patient.

Artificial intelligence serves as an important computational layer within the digital twin architecture. Machine learning algorithms can identify patterns across high-dimensional clinical datasets, while deep learning can analyze imaging, pathology, and other complex data. Natural language processing can extract clinically meaningful information from electronic health records, pathology reports, operative notes, and endoscopy reports. Multimodal models can potentially combine these different data types into unified representations of disease.

The final component is the simulation and decision-support layer. This component uses the patient's digital representation to estimate outcomes under alternative treatment scenarios. Instead of asking only whether a patient is likely to survive, the system could evaluate multiple clinically meaningful outcomes, including tumor response, recurrence risk, progression-free sur-

vival, overall survival, postoperative complications, treatment-related toxicity, quality of life, and functional outcomes. The digital twin could then compare different treatment pathways and provide clinicians with individualized estimates. Importantly, the digital twin should function as a decision-support system rather than an autonomous replacement for clinical judgment. Its recommendations must remain interpretable, clinically validated, and subject to multidisciplinary evaluation.

Digital Twins In Esophageal, Gastric, And Colorectal Cancers

Esophageal, gastric, and colorectal cancers provide important opportunities for the application of digital twin technology because treatment decisions frequently depend on disease stage, anatomical characteristics, molecular features, and response to therapy. In esophageal cancer, treatment may involve endoscopic intervention, surgery, chemotherapy, radiotherapy, immunotherapy, or combinations of these modalities. A digital twin could integrate endoscopic findings, imaging, pathology, nutritional status, and treatment response to simulate alternative treatment pathways. For patients receiving neoadjuvant therapy, serial imaging and clinical data could be used to update the digital representation and estimate the probability of achieving an adequate response before surgery.

Gastric cancer presents similar challenges, particularly because patients with apparently similar disease stages can experience substantially different clinical trajectories. Molecular classification has demonstrated the biological heterogeneity of gastric tumors, while differences in immune characteristics and treatment sensitivity can influence outcomes. A digital twin could integrate molecular profiles with imaging, pathology, and clinical information to estimate the likely benefit of chemotherapy, targeted therapy, immunotherapy, or surgical treatment. This could support more individualized treatment selection and potentially reduce exposure to ineffective therapies.

Colorectal cancer may represent one of the most promising applications of digital twins because treatment decisions often involve multiple sequential interventions. A patient may undergo surgery, chemotherapy, radiotherapy, targeted treatment, immunotherapy, or combinations of these approaches depending on tumor location, stage, molecular characteristics, and response. In rectal cancer, for example, digital twins could simulate different neoadjuvant strategies and estimate the probability of tumor regression, pathological complete response, local recurrence, distant metastasis, and organ preservation.

Digital twins may also improve surveillance

after treatment. Current surveillance strategies generally use predefined schedules for imaging, laboratory testing, endoscopy, and clinical assessment. A dynamic digital twin could theoretically estimate an individual's changing probability of recurrence and adjust surveillance intensity accordingly. Patients with rapidly increasing risk could undergo earlier imaging or additional diagnostic assessment, whereas patients with consistently low predicted risk might avoid unnecessary procedures.

Another important application is the simulation of surgical outcomes. Three-dimensional representations of tumor anatomy could be integrated with patient-specific information to assist surgical planning. For colorectal and gastric cancers, the digital twin could represent tumor location, vascular anatomy, surrounding structures, and anticipated resection margins. Simulation could help multidisciplinary teams evaluate the potential consequences of different surgical approaches. In complex cases, this may contribute to more precise planning and improved communication between surgeons, radiologists, oncologists, and other specialists.

The integration of longitudinal treatment information is particularly important. Instead of representing the patient at a single point in time, the digital twin can continuously incorporate new evidence. A tumor that initially

appears likely to respond to therapy may later demonstrate resistance through imaging or biomarker changes. Updating the digital twin with this information could modify the predicted benefits of continuing the same treatment and identify alternative strategies. This dynamic approach has the potential to transform gastrointestinal cancer care from predominantly stage-based treatment toward continuously personalized management.

Digital Twins In Hepatobiliary And Pancreatic Cancers

Hepatobiliary and pancreatic cancers are particularly suitable for digital twin applications because they involve complex anatomy, substantial biological heterogeneity, and treatment decisions that often depend on multiple interacting variables. Hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, and pancreatic ductal adenocarcinoma frequently require multidisciplinary management involving hepatobiliary surgeons, medical oncologists, radiation oncologists, interventional radiologists, gastroenterologists, pathologists, and other specialists. A digital twin could provide a common computational representation of the patient and facilitate integration of information generated by these different disciplines.

In hepatocellular carcinoma, treatment selection

depends on tumor burden, vascular invasion, liver function, portal hypertension, performance status, and the presence of extrahepatic disease. A digital twin could integrate these variables with imaging and laboratory measurements to simulate the expected consequences of different treatment strategies. For example, it could estimate the potential benefits and risks of resection, ablation, transarterial treatment, radiotherapy, or systemic therapy. Because liver function can change substantially during disease progression and treatment, the digital twin could also update its representation over time.

The potential application in pancreatic cancer is especially important because pancreatic tumors frequently exhibit aggressive biology and complex relationships with major blood vessels. Determining whether a tumor is resectable, borderline resectable, or locally advanced often requires detailed anatomical assessment. A patient-specific digital twin could combine high-resolution imaging with clinical and molecular information to model tumor progression and evaluate possible treatment pathways. It could also support surgical planning by representing the relationship between the tumor and surrounding vascular structures.

Treatment response simulation may be particularly valuable in pancreatic cancer. Neoadjuvant therapy is increasingly important for selected

patients, but the optimal treatment strategy may differ according to tumor biology and patient characteristics. A digital twin could incorporate serial imaging, tumor biomarkers, nutritional status, treatment toxicity, and molecular data to estimate whether continued systemic therapy is likely to provide meaningful benefit or whether a patient may become an appropriate surgical candidate.

For cholangiocarcinoma and gallbladder cancer, digital twins could similarly integrate anatomical imaging, pathology, molecular characteristics, biliary obstruction, liver function, and systemic disease. These cancers often present with complicated anatomical and clinical features, making individualized treatment planning difficult. Digital simulation could allow clinicians to compare alternative approaches and identify strategies that maximize the probability of disease control while minimizing complications.

Another important feature is the potential integration of functional information. Patients with hepatobiliary and pancreatic malignancies may experience malnutrition, impaired liver function, biliary obstruction, pancreatic insufficiency, weight loss, and systemic inflammation. These factors can substantially influence treatment tolerance and outcomes. A comprehensive digital twin should therefore represent not only the tumor but also the patient's physiological

condition. This broader perspective could improve prediction of postoperative complications, treatment-related toxicity, and functional recovery.

Artificial Intelligence, Imaging, And Multi-Omics Integration

Artificial intelligence is central to the development of advanced digital twins because gastrointestinal oncology generates extremely heterogeneous datasets. Conventional statistical approaches are often limited when large numbers of variables interact in nonlinear ways. Machine learning and deep learning can identify complex relationships between clinical characteristics, imaging features, molecular biomarkers, treatment exposures, and outcomes. When integrated into a digital twin, these approaches can create a continuously updated computational model of disease.

Radiomics is particularly relevant because medical imaging contains quantitative information that may not be readily apparent during conventional visual interpretation. Features related to tumor shape, texture, intensity, heterogeneity, vascularity, and spatial relationships can potentially provide information about tumor biology and treatment response. Deep learning models can also extract higher-order imaging representations directly from computed tomography,

magnetic resonance imaging, positron emission tomography, and ultrasound. These features could be incorporated into the digital twin to improve individualized prediction.

Pathology represents another important source of information. Digitized histopathological slides can be analyzed using artificial intelligence to identify tumor architecture, cellular morphology, stromal characteristics, immune-cell patterns, and other features. Combining computational pathology with radiomics may provide complementary information about the same tumor. A digital twin could integrate these modalities and potentially generate a more complete representation of tumor phenotype.

Multi-omics integration adds another layer of biological information. Genomics can identify mutations and structural alterations, transcriptomics can characterize gene-expression patterns, proteomics can provide information about protein activity, and metabolomics can describe biochemical processes. These data may help explain why tumors with similar anatomical stages respond differently to treatment. Incorporating multi-omics information into a digital twin could therefore improve prediction of treatment sensitivity and resistance.

Artificial intelligence can also support longitudinal learning. When new patient data become available, predictive models can be recalibrated

to reflect the evolving disease state. This is important because gastrointestinal tumors can undergo substantial biological changes during treatment. A molecular profile obtained at diagnosis may not fully represent the tumor after chemotherapy, radiotherapy, targeted therapy, or immunotherapy. A dynamic digital twin can potentially incorporate new biopsy, imaging, or biomarker information and update its predictions accordingly.

However, multimodal integration introduces substantial technical challenges. Data generated by different hospitals may use different standards, imaging protocols, laboratory reference ranges, terminology, and electronic health record structures. Missing data are common, while longitudinal observations may be irregularly spaced. Artificial intelligence systems must therefore be designed to handle incomplete and heterogeneous information. External validation across institutions and patient populations is essential to ensure that digital twins generalize beyond the datasets used for development.

Explainability is also critical. Clinicians need to understand why a digital twin predicts that one treatment is more appropriate than another. Models that provide only opaque probabilities may be difficult to trust in high-stakes clinical settings. Future systems should therefore combine predictive performance with interpretable

outputs, uncertainty estimates, and clinically meaningful explanations. This will be essential for translating artificial intelligence-driven digital twins from experimental research into routine gastrointestinal oncology practice.

Adaptive Treatment And Personalized Clinical Decision-Making

One of the most important potential advantages of digital twins is their ability to support adaptive treatment. Traditional treatment planning usually relies heavily on information available at diagnosis. Although treatment may subsequently be modified, decisions are often based on relatively limited reassessment. A digital twin could provide continuous evaluation by incorporating new information after each clinically important event. This creates the possibility of treatment strategies that evolve according to the patient's actual response.

In gastrointestinal cancers, adaptive treatment could be particularly valuable during neoadjuvant therapy. Serial imaging, laboratory measurements, symptoms, circulating biomarkers, and treatment tolerance could be incorporated into the digital twin. The system could estimate whether the tumor is responding as expected and compare the predicted outcomes of continuing, intensifying, changing, or stopping treatment. Such an approach could reduce prolonged

exposure to ineffective therapies.

Digital twins could also support individualized treatment intensity. Two patients with the same anatomical stage may have different risks of recurrence, toxicity, or treatment failure. A patient with a high probability of recurrence might benefit from more intensive systemic treatment or closer surveillance, whereas a patient with a favorable biological profile might potentially avoid unnecessary treatment. These decisions would require rigorous clinical evidence, but digital twins could provide a computational framework for evaluating them.

Quality of life should also become an integral component of digital twin-based decision-making. Treatment decisions in gastrointestinal oncology can influence bowel function, nutritional status, pain, fatigue, physical activity, sexual function, and psychological well-being. A treatment associated with slightly better disease control may not necessarily be preferable if it causes substantial long-term functional impairment for a particular patient. Digital twins could incorporate patient-reported outcomes and estimate both oncological and functional consequences of different strategies.

Shared decision-making could therefore become more individualized. Rather than presenting patients with general population-level outcomes, clinicians could use a digital twin to illustrate

how different treatment options may affect an individual patient's predicted outcomes. For example, a patient could compare the estimated probabilities of recurrence, treatment toxicity, postoperative complications, and quality-of-life outcomes under different treatment pathways. This could facilitate clearer discussions between patients and multidisciplinary teams.

Digital twins may also support multidisciplinary tumor boards. Complex gastrointestinal cancers frequently require integration of surgical, oncological, radiological, pathological, and gastroenterological expertise. A digital twin could organize relevant patient information and generate a standardized computational summary. It could then simulate alternative strategies for discussion by the tumor board. Such systems may improve consistency and reduce the risk that important information is overlooked.

Importantly, adaptive digital twin systems should not automatically change treatment without clinical oversight. Predictions are probabilistic and may be affected by data quality, model limitations, and unexpected biological events. The appropriate role of the digital twin is to provide continuously updated evidence that supports clinicians and patients in making informed decisions. Prospective clinical trials will be required to determine whether this approach improves survival, quality of life, treatment efficiency, or other meaningful outcomes.

Challenges, Ethical Considerations, And Clinical Validation

Despite their substantial potential, digital twins for gastrointestinal cancer face important scientific, technical, clinical, ethical, and regulatory challenges. The first challenge is data quality. Digital twins depend on accurate and sufficiently complete information, yet clinical datasets frequently contain missing values, inconsistent documentation, measurement errors, and variations in diagnostic practice. Imaging protocols may differ between institutions, pathology interpretation may vary between observers, and electronic health records often contain unstructured information. These limitations can directly affect model performance.

Generalizability represents another major concern. A digital twin developed using data from a single cancer center may perform well in its development population but poorly in other settings. Differences in patient demographics, disease prevalence, healthcare systems, treatment practices, and diagnostic technologies can produce substantial changes in model behavior. Multicenter datasets and external validation are therefore essential. Prospective validation should determine whether digital twin-guided decisions actually improve clinical outcomes ra-

ther than merely demonstrating statistical prediction accuracy.

Bias must also be carefully addressed. If training datasets underrepresent specific populations, the resulting digital twin may provide less accurate predictions for those patients. This is particularly important in global gastrointestinal oncology because access to molecular testing, advanced imaging, surgery, and systemic therapy varies considerably between countries and healthcare systems. Digital twin development should therefore prioritize representative datasets and transparent evaluation of model performance across clinically relevant subgroups.

Privacy and data governance are equally important. Digital twins may contain highly sensitive information, including genetic profiles, pathology, imaging, treatment histories, and longitudinal health records. Secure data storage, controlled access, encryption, and appropriate governance mechanisms are necessary. Patients should understand how their data are being used, particularly when information contributes to artificial intelligence model development.

The question of responsibility is another important ethical issue. If a digital twin recommends a treatment strategy and the patient experiences an adverse outcome, responsibility must remain clearly defined. Clinicians should not be expected to follow algorithmic rec-

ommendations automatically, particularly when clinical circumstances conflict with model predictions. Digital twins should therefore provide transparent outputs, uncertainty estimates, and information about the evidence supporting their predictions.

Regulatory frameworks will need to evolve alongside these technologies. A digital twin that continuously learns from new patient information may behave differently from a static medical device. Continuous updating can improve performance but may also introduce new risks. Appropriate mechanisms for monitoring, recalibration, version control, and post-deployment evaluation will therefore be necessary.

Finally, clinical validation should focus on patient-centered outcomes. High discrimination or calibration alone is insufficient. Trials should determine whether digital twin-guided care improves overall survival, progression-free survival, recurrence rates, treatment toxicity, quality of life, patient satisfaction, and healthcare efficiency. Economic evaluations should also assess whether the additional computational infrastructure is justified by clinical benefits. Only through rigorous prospective evaluation can digital twins move from an attractive technological concept to a reliable component of gastrointestinal cancer care.

Future Perspectives And Conclusion

The future of digital twins in gastrointestinal oncology is likely to involve increasingly sophisticated integration of artificial intelligence, multi-omics, medical imaging, computational pathology, electronic health records, wearable technologies, and real-time physiological information. Instead of representing the tumor as a static entity, future systems may model the interaction between tumor biology, host physiology, treatment exposure, immune responses, and environmental factors. This could create a more comprehensive representation of the patient and provide a stronger foundation for personalized cancer treatment.

Future digital twins may also incorporate mechanistic models alongside machine learning. Purely data-driven algorithms can identify predictive patterns, but mechanistic models can provide representations of biological processes such as tumor growth, treatment resistance, immune interactions, and drug response. Combining these approaches could improve both predictive performance and interpretability. Hybrid models may allow clinicians to examine not only what is likely to happen but also potential biological explanations for different treatment responses.

Real-time monitoring could further transform this field. Wearable devices, remote symptom reporting, home-based physiological measurements, and repeated laboratory or molecular assessments may provide continuous information about patient status. Integration of these data into a digital twin could allow earlier identification of treatment toxicity, nutritional deterioration, infection, or disease progression. This could shift gastrointestinal oncology toward proactive management rather than episodic clinical assessment.

Digital twins may eventually support highly individualized treatment experimentation through virtual clinical trials. Before a treatment is administered, alternative strategies could be simulated using the patient's computational representation. Although such simulations cannot replace prospective clinical trials, they may help prioritize treatment options and identify patients who are most likely to benefit from specific interventions. At the population level, aggregated digital twins could also support clinical research by identifying patterns of treatment response and generating hypotheses for future trials.

The integration of digital twins with precision oncology may be particularly transformative for cancers characterized by substantial heterogeneity and limited treatment options. Pan-

creatic cancer, advanced colorectal cancer, hepatocellular carcinoma, cholangiocarcinoma, and other aggressive gastrointestinal malignancies may benefit from systems capable of identifying individualized therapeutic opportunities and detecting resistance earlier. For cancers with more established treatment pathways, digital twins may improve treatment selection, surveillance, surgical planning, and quality-of-life optimization.

Nevertheless, technological sophistication should not be mistaken for clinical effectiveness. The central objective must remain improving outcomes that matter to patients. Digital twins should therefore be developed through multidisciplinary collaboration involving clinicians, data scientists, engineers, statisticians, patients, ethicists, and healthcare policymakers. Transparent validation, robust data governance, external testing, and prospective clinical evaluation will be essential for responsible implementation.

In conclusion, digital twins represent a promising next-generation approach to gastrointestinal cancer treatment. By integrating clinical information, imaging, pathology, molecular data, artificial intelligence, and longitudinal outcomes, they can potentially create dynamic patient-specific models capable of simulating disease progression and treatment response. Their greatest potential lies in enabling continuous,

adaptive, and personalized decision-making rather than relying exclusively on population-level treatment strategies. If the current challenges surrounding data quality, interoperability, bias, privacy, interpretability, regulation, and clinical validation are successfully addressed, digital twins could become an important component of precision gastrointestinal oncology. Their development may ultimately support a new model of cancer care in which treatment is continuously optimized according to the evolving biological and clinical characteristics of each individual patient.

7. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN PROSTATE AND GENITOURINARY CANCERS

Background

Prostate and genitourinary cancers represent a diverse group of malignancies involving the prostate, kidney, urinary bladder, testis, penis, and upper and lower urinary tract. These cancers differ substantially in their molecular characteristics, patterns of progression, anatomical behavior, treatment responses, and clinical outcomes. Although advances in surgery, radiotherapy, systemic therapy, immunotherapy, targeted therapy, molecular diagnostics, and minimally invasive procedures have significantly improved cancer management, substantial challenges remain. Patients with apparently similar disease stages can experience markedly different treatment responses, recurrence risks, adverse effects, and long-term outcomes. This heterogeneity has created a strong need for more individualized approaches capable of integrating the multiple dimensions of modern cancer care.

Digital twin technology represents an emerging approach that may contribute to this transformation. A digital twin is a dynamic computational representation of an individual patient that is continuously informed by clinical and

biological data. Unlike a conventional risk prediction model, which often generates a prediction at a single point in time, a digital twin can potentially evolve as the patient's disease and treatment course change. In prostate and genitourinary oncology, such a system could integrate demographic characteristics, medical history, laboratory findings, imaging, pathology, genomic information, treatment exposure, adverse events, and longitudinal outcomes. Artificial intelligence can then analyze these data and simulate potential disease trajectories and responses to alternative treatment strategies.

The potential relevance of digital twins is particularly evident in prostate cancer. Clinical management can involve active surveillance, focal treatment, surgery, radiotherapy, androgen deprivation therapy, androgen receptor pathway inhibitors, chemotherapy, radioligand therapy, immunotherapy, or combinations of these approaches. The appropriate strategy depends not only on disease stage but also on tumor grade, prostate-specific antigen kinetics, imaging findings, genomic characteristics, patient age, comorbidities, life expectancy, and personal preferences. A digital twin could potentially simulate these treatment pathways and estimate their expected benefits and risks for an individual patient.

Similar opportunities exist across other genitourinary malignancies. In bladder cancer, clin-

icians must determine whether patients with non-muscle-invasive disease require intravesical treatment, intensified surveillance, or radical intervention, while patients with muscle-invasive disease may require multimodal treatment involving neoadjuvant chemotherapy, radical cystectomy, radiotherapy, immunotherapy, or bladder-preserving approaches. Kidney cancer management can involve active surveillance, partial or radical nephrectomy, ablation, immunotherapy, targeted therapy, and combinations of systemic treatments. Testicular cancer requires treatment decisions that carefully balance excellent cure rates with long-term treatment-related morbidity.

Digital twins may therefore enable a new model of genitourinary cancer care in which treatment is continuously adapted according to changing disease characteristics. Serial imaging, biomarkers, pathology, treatment response, and patient-reported outcomes could update the digital representation over time. This approach could facilitate earlier identification of treatment resistance, optimize treatment sequencing, and support shared decision-making. The ultimate goal is not to replace clinicians but to provide a comprehensive computational framework for individualized, evidence-informed treatment planning.

Digital Twin Architecture

For Prostate And Genito-urinary Cancer Care

The development of digital twins for prostate and genitourinary cancers requires integration of multiple layers of clinical, anatomical, biological, and longitudinal information. The foundation is a comprehensive patient data layer containing demographic characteristics, age, comorbidities, family history, previous treatments, medications, performance status, renal function, hormonal status, symptoms, and other relevant clinical characteristics. These variables influence treatment eligibility, expected tolerance, and long-term outcomes and therefore need to be represented within the patient's digital model.

Imaging is another fundamental component. Prostate cancer evaluation increasingly relies on multiparametric magnetic resonance imaging, which provides information about lesion location, tumor extent, and relationships with surrounding structures. Computed tomography, bone imaging, positron emission tomography, and prostate-specific membrane antigen imaging can provide additional information about metastatic disease. In kidney and bladder cancers, computed tomography and magnetic resonance imaging provide information about tumor anatomy, local invasion, vascular involvement, and distant disease. A digital twin can combine these imaging data to construct a more

comprehensive representation of the patient's disease.

Pathological information provides another critical layer. In prostate cancer, Gleason grade group, tumor volume, pathological stage, surgical margins, extracapsular extension, and seminal vesicle involvement contribute to prognosis. In bladder cancer, histological subtype, tumor grade, depth of invasion, lymphovascular invasion, carcinoma in situ, and nodal status influence treatment decisions. Similar pathological characteristics are important in renal, testicular, and other genitourinary malignancies. Digital pathology and artificial intelligence can potentially extract additional information from whole-slide images, including tumor architecture, cellular morphology, stromal characteristics, and immune-cell patterns.

Molecular data can further characterize tumor biology. Genomic alterations, DNA repair abnormalities, androgen receptor signaling, immune-related biomarkers, and other molecular characteristics may influence treatment selection. In prostate cancer, genomic classifiers and alterations in DNA repair pathways may provide information about prognosis and potential therapeutic sensitivity. In urothelial and renal cancers, molecular characteristics may help explain differences in response to targeted and immune-based therapies.

The computational layer of the digital twin can

employ machine learning, deep learning, natural language processing, and mechanistic modeling. Natural language processing can extract information from pathology reports, radiology reports, operative notes, and oncology records. Deep learning can analyze imaging and pathology. Machine learning can integrate clinical and molecular variables into individualized predictions. Mechanistic models can represent tumor growth, treatment effects, and disease progression.

The final layer is a simulation and decision-support environment. It can compare potential treatment strategies and estimate outcomes such as tumor response, biochemical recurrence, metastatic progression, survival, treatment toxicity, postoperative complications, urinary function, sexual function, renal function, and quality of life. The system should also communicate uncertainty rather than presenting predictions as absolute outcomes. A clinically useful digital twin should therefore provide individualized estimates that can be interpreted and critically evaluated by multidisciplinary clinical teams.

Digital Twins In Prostate Cancer

Prostate cancer may represent one of the most important applications of digital twin technology because its clinical course is highly heterogeneous and treatment decisions often involve competing risks. Some tumors remain

indolent for many years, whereas others progress rapidly and develop metastatic or castration-resistant disease. A digital twin could integrate prostate-specific antigen measurements, multiparametric magnetic resonance imaging, biopsy findings, Gleason grade group, tumor volume, genomic information, family history, age, comorbidities, and treatment history to generate an individualized representation of disease.

Active surveillance is a particularly important area for digital twin applications. Many men with low-risk or selected intermediate-risk prostate cancer can avoid immediate definitive treatment, but surveillance requires repeated assessment and timely recognition of disease progression. A digital twin could continuously incorporate prostate-specific antigen kinetics, repeat imaging, biopsy findings, and other biomarkers to estimate the probability of clinically significant progression. Instead of applying identical surveillance schedules to all patients, the intensity and timing of follow-up could potentially be personalized according to the patient's evolving risk.

For patients requiring definitive treatment, digital twins could simulate the potential consequences of surgery and radiotherapy. Radical prostatectomy can provide excellent cancer control but may result in urinary incontinence and erectile dysfunction. Radiotherapy can similarly provide effective disease control while producing

acute and long-term toxicities. A digital twin could incorporate anatomical, clinical, and functional characteristics to estimate the likely oncological and quality-of-life consequences of each treatment pathway. Such information could support shared decision-making between patients and clinicians.

The technology could also contribute to treatment planning. Three-dimensional patient-specific models generated from imaging could represent the prostate, tumor locations, neurovascular structures, urethra, bladder, rectum, and other relevant anatomical structures. These models could potentially assist surgical planning and radiotherapy optimization. Artificial intelligence could further identify imaging patterns associated with aggressive disease or treatment response.

Advanced prostate cancer represents another important application. Patients with metastatic hormone-sensitive prostate cancer may receive androgen deprivation therapy combined with androgen receptor pathway inhibitors or chemotherapy. As the disease progresses, treatment options may include additional hormonal agents, chemotherapy, radioligand therapy, targeted treatments, or selected immunotherapies. A digital twin could model the patient's disease trajectory and simulate potential sequencing strategies.

Castration-resistant prostate cancer is particu-

larly suited to adaptive digital twin approaches because resistance may develop through complex biological mechanisms. Changes in prostate-specific antigen, imaging, symptoms, circulating biomarkers, and molecular characteristics could update the digital model. The system could estimate whether continued therapy is likely to provide meaningful benefit or whether an alternative strategy should be considered.

Digital twins could also integrate patient preferences into prostate cancer treatment decisions. The relative importance of cancer control, urinary function, sexual function, treatment burden, travel requirements, and other personal priorities differs substantially among individuals. A truly patient-centered digital twin should therefore represent both disease characteristics and patient-defined outcomes. This could transform prostate cancer management from selecting a treatment based primarily on disease category toward selecting a strategy that best aligns expected oncological outcomes with individual priorities.

Digital Twins In Bladder, Kidney, And Other Genitourinary Cancers

Digital twins may have similarly important applications in bladder, kidney, and other genitourinary malignancies. Bladder cancer is characterized by considerable clinical heterogeneity, particularly between non-muscle-invasive and

muscle-invasive disease. In non-muscle-invasive bladder cancer, decisions regarding transurethral resection, intravesical therapy, repeat resection, maintenance treatment, and surveillance are influenced by tumor grade, stage, size, multiplicity, recurrence history, and other clinical factors. A digital twin could incorporate these variables with cystoscopic, pathological, molecular, and imaging data to estimate individualized recurrence and progression risks.

The dynamic nature of bladder cancer makes longitudinal modeling particularly relevant. Patients often undergo repeated cystoscopy, urine testing, imaging, biopsies, and intravesical treatment. Each new observation can update the computational representation of disease. A digital twin could therefore estimate whether the probability of recurrence or progression has changed and whether surveillance intensity or treatment strategy should be modified. It could also potentially identify patients who are unlikely to benefit from prolonged ineffective intravesical treatment.

In muscle-invasive bladder cancer, digital twins could support decisions between radical cystectomy and bladder-preserving strategies. Neoadjuvant chemotherapy, chemoradiotherapy, immunotherapy, surgery, and other approaches may be considered depending on disease characteristics and patient suitability. The digital twin could integrate tumor stage, imaging, pathological features, renal function, comorbidities, treatment response, and patient preferences to simulate alternative pathways. Serial imaging during neoadjuvant treatment could provide information about response and help estimate the probability of successful bladder preservation or the need for definitive surgery.

Renal cell carcinoma also provides important opportunities. Small renal masses may be managed through active surveillance, partial nephrectomy, radical nephrectomy, or ablation. Treatment selection depends on tumor size, location, growth rate, patient age, renal function, comorbidities, and competing mortality risks. A digital twin could simulate the likely consequences of each approach, including tumor progression, renal function decline, postoperative complications, and long-term survival.

For advanced renal cell carcinoma, systemic treatment increasingly involves combinations of immune checkpoint inhibitors and targeted therapies. Individual responses vary substantially, and treatment-related toxicity can be significant. A digital twin could integrate tumor characteristics, immune biomarkers, treatment history, laboratory findings, and longitudinal response to estimate the probability of benefit from alternative systemic regimens.

Testicular cancer presents a different but highly relevant use case. Because many patients can be cured, long-term toxicity becomes an important

component of treatment selection. A digital twin could help simulate the balance between cancer control and risks associated with chemotherapy, radiotherapy, surgery, or surveillance. Similar approaches could be considered for penile cancer, upper tract urothelial carcinoma, and other rare genitourinary malignancies, where limited patient numbers make individualized computational modeling particularly attractive.

Artificial Intelligence, Imaging, And Multi-Omics Integration

Artificial intelligence is a central component of next-generation digital twins because genitourinary oncology produces large quantities of heterogeneous data. Imaging, pathology, laboratory measurements, molecular profiles, treatment records, and patient-reported outcomes provide complementary information about disease biology. Integrating these data using artificial intelligence could enable more accurate and dynamic representations of individual patients.

Radiomics is particularly relevant in prostate, kidney, and bladder cancers. Imaging contains quantitative characteristics related to tumor texture, shape, intensity, heterogeneity, vascularity, and spatial relationships that may provide information beyond conventional visual assessment. Deep learning can identify complex imaging patterns and potentially predict clinically significant prostate cancer, treatment response,

recurrence, or metastatic progression. When incorporated into a digital twin, these features can contribute to a continuously updated representation of tumor behavior.

Computational pathology offers another major opportunity. Whole-slide images can be analyzed using artificial intelligence to identify morphological characteristics associated with tumor aggressiveness, immune infiltration, stromal composition, and treatment response. In prostate cancer, computational analysis may complement Gleason grading and other pathological assessments. In bladder and renal cancers, digital pathology may provide additional information about tumor heterogeneity and biological behavior.

Multi-omics integration can further enhance the digital twin. Genomic data can identify mutations and structural alterations, transcriptomic information can characterize gene expression, proteomics can describe protein activity, and metabolomics can provide insight into cellular metabolism. These layers may help distinguish tumors that appear similar anatomically but behave differently biologically.

The integration of immune-related information is particularly important for genitourinary cancers because immunotherapy plays a major role in bladder and renal cancer and an expanding role in selected prostate cancer settings. A digital twin could potentially combine tumor gen-

omic characteristics, immune-cell patterns, circulating biomarkers, and treatment history to estimate the likelihood of response to immune-based therapies.

Artificial intelligence can also facilitate longitudinal learning. A patient's digital twin can be updated whenever new data become available. For example, changes in prostate-specific antigen, prostate imaging, or biopsy findings can alter the predicted trajectory of localized prostate cancer. Similarly, new imaging or laboratory findings in metastatic renal or bladder cancer can change estimates of treatment response.

However, multimodal artificial intelligence systems must address substantial technical challenges. Data generated at different institutions often differ in quality, formatting, imaging protocols, terminology, and clinical practice. Missing data and irregular follow-up are common. Models must therefore be designed to accommodate incomplete longitudinal information and should undergo external validation across diverse healthcare settings.

Interpretability is equally important. Clinicians need to understand which features contribute to a prediction and how uncertainty affects the recommendation. Digital twins should provide clinically meaningful explanations rather than simply producing a numerical risk score. Transparent models, uncertainty estimates, sensitivity analyses, and visual representations of relevant

patient data may improve clinician confidence and facilitate responsible adoption.

Adaptive Treatment And Personalized Clinical Decision-Making

A major advantage of digital twins is their potential to transform treatment from a predominantly static process into an adaptive strategy. In conventional cancer care, treatment is usually selected according to information available at diagnosis, with subsequent modifications based on predefined clinical criteria. A digital twin could continuously evaluate the patient's evolving disease state and estimate whether the current strategy remains optimal.

In prostate cancer, adaptive treatment could be used during active surveillance, radiation therapy, systemic therapy, and management of metastatic disease. Serial prostate-specific antigen measurements, imaging, biopsy findings, treatment toxicity, and patient-reported outcomes could update the digital twin. If the predicted probability of progression increases, the system could identify whether definitive treatment or a different systemic approach should be considered.

In advanced prostate cancer, treatment sequencing is particularly complex. Several agents may provide benefit, but their effectiveness depends on previous treatments, disease biology, molecular alterations, and patient condition. A digital

twin could compare potential sequences and estimate expected outcomes under each scenario. This could help clinicians consider not only the immediate response but also the longer-term consequences of treatment choices.

Adaptive management may be equally important in bladder cancer. Patients receiving intravesical treatment could be monitored through cystoscopy, urine biomarkers, pathology, and clinical information. Changes in the digital twin could identify patients at increasing risk of progression and support consideration of more intensive treatment. In muscle-invasive disease, response to neoadjuvant treatment could inform the predicted benefit of continuing the current approach versus proceeding to surgery or another treatment strategy.

In kidney cancer, digital twins could support decisions involving surveillance versus intervention for localized disease and treatment sequencing for advanced disease. For patients with small renal masses, changes in tumor growth rate and renal function could be continuously incorporated into the model. This could help balance the risk of cancer progression against the consequences of intervention.

Quality of life should be integrated into adaptive decision-making. Genitourinary cancer treatments can affect urinary continence, sexual function, fertility, renal function, bowel function, fatigue, and psychological well-being. A

digital twin that focuses exclusively on survival would therefore provide an incomplete representation of the patient's needs. Patient-reported outcomes should be incorporated into the computational model so that treatment decisions reflect both oncological and functional outcomes.

Digital twins could also facilitate shared decision-making by presenting individualized treatment scenarios. Patients could receive understandable estimates of the potential benefits and risks associated with different options. For example, a patient with localized prostate cancer could compare predicted cancer control with estimated risks of urinary and sexual complications under different treatment strategies. A patient with a small renal mass could compare surveillance with intervention while considering both oncological risk and potential renal function loss.

The role of clinicians remains central. Digital twins should provide evidence and simulations rather than make autonomous treatment decisions. Their outputs should be reviewed by appropriate specialists, particularly when predictions are uncertain or when the patient's clinical circumstances fall outside the model's validated population. Prospective trials will ultimately be needed to determine whether digital twin-guided adaptive care improves meaningful clinical outcomes.

Challenges, Ethical Considerations, And Clinical Validation

The implementation of digital twins in prostate and genitourinary oncology faces significant challenges. One of the most fundamental is data quality. Digital twins depend on accurate and sufficiently complete information, yet clinical records often contain missing values, inconsistent terminology, measurement errors, and incomplete longitudinal follow-up. Imaging protocols and pathological assessments may also vary across institutions. These problems can reduce the reliability of predictions.

Generalizability is another major concern. A model developed using patients from a single institution may not perform equally well in other populations. Differences in ethnicity, disease prevalence, healthcare access, diagnostic technologies, treatment practices, and follow-up strategies can affect model performance. Multicenter development and external validation are therefore essential before clinical implementation.

Bias is particularly important in artificial intelligence systems. If specific patient populations are underrepresented in training datasets, predictions may be less accurate for those groups. Genitourinary cancer digital twins should therefore be evaluated across clinically relevant subgroups, including different age groups, disease

stages, comorbidity profiles, and healthcare settings.

Privacy and data governance represent additional concerns. Digital twins may contain highly sensitive genomic, imaging, pathological, and longitudinal clinical information. Strong cybersecurity, controlled access, encryption, secure data storage, and appropriate consent procedures are essential. Patients should understand how their information is used, particularly when their data contribute to artificial intelligence development.

Another issue involves responsibility for clinical decisions. If a digital twin recommends one treatment strategy and the outcome is unfavorable, it must remain clear that the technology is a decision-support system rather than an autonomous clinical authority. Clinicians must be able to override recommendations when appropriate. Systems should provide uncertainty estimates and identify circumstances in which predictions may be unreliable.

Continuous learning introduces additional regulatory complexity. A static model can be evaluated and approved based on a defined version, whereas a digital twin may change as new information is incorporated. Continuous updates can improve performance but may also introduce unexpected behavior. Robust monitoring, model version control, recalibration, and post-deployment surveillance will therefore be necessary.

Clinical validation should extend beyond technical performance. Measures such as discrimination, calibration, and predictive accuracy are important but insufficient. The ultimate question is whether digital twin-guided treatment improves patient outcomes. Prospective studies should examine survival, recurrence, treatment toxicity, functional outcomes, quality of life, patient satisfaction, and healthcare resource utilization. Randomized trials may be particularly important for determining whether digital twin-based strategies offer advantages over conventional personalized treatment.

Economic evaluation should also be considered. Developing and maintaining digital twins requires computational infrastructure, data integration, specialized personnel, and continuous validation. The technology will be most valuable when its clinical benefits justify these investments. Implementation should therefore be guided by both clinical effectiveness and health-economic evidence.

Future Perspectives And Conclusion

The future of digital twins in prostate and genitourinary oncology is likely to involve increasingly sophisticated integration of clinical, imaging, pathological, molecular, physiological, and patient-reported information. The digital twin may gradually evolve from a predictive

model into a comprehensive computational representation capable of simulating disease progression and treatment response over the entire cancer journey.

One important direction is the integration of mechanistic and artificial intelligence models. Machine learning can identify complex relationships within large datasets, while mechanistic models can represent biological processes such as tumor growth, androgen signaling, immune interactions, and treatment resistance. Combining these approaches could improve interpretability and enable more biologically informed simulations.

Real-time monitoring may further strengthen digital twins. Wearable technologies, remote symptom monitoring, home-based measurements, and repeated laboratory testing could provide continuous information about patient status. In genitourinary cancers, this could include monitoring urinary symptoms, physical activity, treatment-related toxicity, renal function, and patient-reported quality of life. These data could allow earlier detection of clinically meaningful changes.

Virtual treatment simulation may also become increasingly sophisticated. Before administering a treatment, clinicians could potentially use the digital twin to compare alternative therapeutic pathways. In prostate cancer, this might include comparing surveillance, surgery, radiotherapy,

or systemic approaches. In bladder cancer, it might involve comparing bladder-preserving strategies with radical surgery. In kidney cancer, it could help evaluate surveillance, ablation, partial nephrectomy, or systemic treatment. These simulations could support more individualized treatment selection.

Digital twins may also contribute to clinical research. Patient-specific simulations could help identify factors associated with treatment response and generate hypotheses for prospective studies. Aggregated digital twin data could potentially support virtual trial design, treatment optimization, and identification of patient subgroups most likely to benefit from emerging therapies.

For rare genitourinary cancers, digital twins may be particularly valuable because conventional evidence can be limited by small patient populations. Computational integration of international datasets could help improve individualized prediction while supporting research into uncommon tumors. However, such applications will require careful attention to data harmonization, privacy, and external validation.

The long-term objective should be a patient-centered system that combines biological precision with clinical practicality. Digital twins should not simply generate increasingly complex predictions. They should provide information that clinicians and patients can understand

and use. The most valuable systems will therefore integrate accurate prediction, transparent uncertainty, interpretable explanations, and meaningful patient preferences.

In conclusion, digital twins represent a promising next-generation framework for the management of prostate and genitourinary cancers. By integrating imaging, pathology, molecular information, clinical characteristics, treatment exposure, and longitudinal outcomes, these systems could create dynamic representations of individual patients and support simulation of alternative treatment pathways. Their applications may extend from active surveillance and surgical planning to systemic treatment selection, treatment sequencing, recurrence monitoring, and adaptive management of advanced disease.

The greatest potential of digital twins lies in their ability to continuously update treatment decisions as the patient's disease evolves. Instead of relying exclusively on population-level averages or baseline clinical characteristics, future cancer care may use individualized computational models to estimate what is most likely to happen under different treatment scenarios. If challenges involving data quality, interoperability, bias, privacy, interpretability, regulation, and prospective validation can be addressed, digital twins could become an important component of precision genitourinary oncology. Ul-

timately, their successful implementation could support a more adaptive, personalized, and patient-centered model of cancer treatment in which therapeutic decisions evolve alongside the biology and lived experience of each individual patient.

8. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN SKIN AND SOFT TISSUE CANCERS

Background

Skin and soft tissue cancers represent a broad and biologically diverse group of malignancies that includes melanoma, keratinocyte carcinomas, dermatofibrosarcoma protuberans, Merkel cell carcinoma, cutaneous lymphomas, angiosarcoma, and a wide range of soft tissue sarcomas. These cancers differ substantially in their cellular origins, molecular characteristics, anatomical distribution, metastatic patterns, treatment sensitivity, and clinical outcomes. Although advances in prevention, dermoscopy, digital imaging, pathology, surgery, radiotherapy, immunotherapy, targeted therapy, and molecular diagnostics have improved management, substantial challenges remain. Early detection does not always prevent aggressive progression, and advanced disease may demonstrate considerable biological heterogeneity and resistance to treatment. Furthermore, treatment decisions must frequently balance tumor control with preservation of appearance, function, mobility, and quality of life.

Digital twin technology represents an emerging approach that could address several of these

challenges by creating a dynamic computational representation of an individual patient and their disease. Unlike conventional prediction models that typically estimate a single outcome using baseline variables, a digital twin can potentially evolve as new clinical, imaging, pathological, molecular, and treatment information becomes available. In skin and soft tissue oncology, the digital twin could integrate patient characteristics, lesion morphology, dermoscopic images, clinical photographs, histopathological findings, radiological examinations, molecular profiles, treatment exposure, adverse events, and longitudinal outcomes. Artificial intelligence could then analyze these heterogeneous data and simulate alternative treatment strategies.

The potential applications are particularly important in melanoma. Management may involve surgical excision, sentinel lymph node evaluation, adjuvant systemic therapy, immunotherapy, targeted therapy, radiation, or combinations of these approaches. The optimal strategy depends on tumor thickness, ulceration, nodal involvement, molecular alterations, metastatic burden, immune characteristics, and patient-specific factors. A digital twin could potentially simulate different treatment pathways and estimate individualized probabilities of recurrence, response, toxicity, and survival.

Non-melanoma skin cancers provide additional opportunities. Basal cell carcinoma and cutane-

ous squamous cell carcinoma are common, but selected tumors can behave aggressively and produce substantial local morbidity or metastatic disease. Digital twins could support decisions involving surgery, margin selection, radiation, systemic therapy, and surveillance. Merkel cell carcinoma, which is less common but highly aggressive, could benefit from computational models integrating imaging, pathology, immune characteristics, and treatment response.

Soft tissue sarcomas create another complex setting because they include numerous histological subtypes and can arise in almost any anatomical location. Treatment frequently requires multidisciplinary decisions involving surgery, radiotherapy, systemic therapy, and occasionally advanced targeted approaches. Patient-specific computational models could help evaluate the consequences of different treatment sequences and support surgical planning.

The long-term goal of digital twins in skin and soft tissue oncology is therefore not simply to improve prediction. It is to create a dynamic framework for personalized treatment in which disease evolution, treatment response, functional outcomes, and patient preferences are continuously integrated. Such systems could facilitate earlier recognition of treatment resistance, more precise treatment selection, adaptive therapy, and individualized surveillance. Their successful implementation could contribute to

a new model of cancer care in which treatment strategies evolve with the patient rather than remaining fixed after the initial diagnosis.

Digital Twin Architecture For Skin And Soft Tissue Cancer Care

A digital twin for skin and soft tissue cancer requires an architecture capable of integrating information from multiple clinical and technological sources. The first layer is the patient data component, which includes demographic characteristics, age, sex, comorbidities, family history, previous malignancies, medications, immune status, performance status, lifestyle characteristics, and previous treatments. These factors may influence both disease behavior and treatment tolerance and should therefore be incorporated into individualized modeling.

The second layer involves direct clinical assessment and digital imaging. Dermatological cancers are particularly suitable for image-based digital twin development because lesions can be repeatedly photographed and evaluated over time. Standardized clinical photographs, dermoscopic images, total-body photography, and other digital imaging techniques can provide information about lesion size, shape, color, vascular patterns, border characteristics, and temporal changes. Artificial intelligence can extract quantitative features from these images and incorporate them into the digital representation.

Histopathology constitutes another essential component. Skin and soft tissue tumors can demonstrate substantial morphological heterogeneity, and histopathological characteristics frequently determine diagnosis, grade, prognosis, and treatment selection. Digitized whole-slide images can be analyzed using computational pathology methods to identify tumor architecture, cellular morphology, necrosis, mitotic activity, stromal characteristics, vascular invasion, and immune-cell patterns. Integrating these features with clinical and imaging data may provide a more complete representation of tumor biology.

Radiological data become particularly important for deeper soft tissue tumors and advanced cutaneous malignancies. Magnetic resonance imaging can characterize soft tissue sarcomas in detail, while computed tomography and positron emission tomography can provide information about local invasion and distant metastases. Serial imaging can also reveal treatment-induced changes and disease progression. A digital twin could integrate these examinations longitudinally to estimate changes in tumor burden and biological behavior.

Molecular information forms another layer. Genomic alterations, gene expression, epigenetic characteristics, immune-related biomarkers, and other molecular features may provide insight into tumor behavior and treatment sen-

sitivity. In melanoma, for example, alterations involving signaling pathways can influence targeted treatment selection. Similar molecular information can contribute to treatment decisions in sarcomas and other rare skin tumors.

The computational layer combines artificial intelligence with statistical and mechanistic modeling. Machine learning can integrate clinical variables and biomarkers, while deep learning can analyze images and pathology. Natural language processing can extract relevant information from clinical notes, pathology reports, operative records, and oncology documentation. Mechanistic models can complement data-driven approaches by representing tumor growth, treatment response, and disease progression.

The final layer is the clinical simulation environment. This component can compare potential treatment pathways and estimate outcomes such as local control, recurrence, metastasis, survival, treatment toxicity, functional impairment, cosmetic outcomes, and quality of life. Importantly, the system should represent uncertainty and allow clinicians to examine the factors influencing predictions. A digital twin should function as a clinical decision-support system, not as an autonomous replacement for medical expertise.

Digital Twins In Melanoma

And Advanced Skin Cancers

Melanoma is one of the most promising areas for digital twin applications because it demonstrates substantial biological heterogeneity and can undergo rapid progression in advanced disease. The clinical course of melanoma varies considerably among patients, even when tumors appear similar according to conventional staging. A digital twin could integrate lesion characteristics, dermoscopic and photographic findings, histopathology, molecular information, imaging, treatment history, and longitudinal biomarkers to construct an individualized representation of the disease.

Early melanoma management could benefit from digital twins through improved risk assessment and surveillance. Serial clinical and dermoscopic images could be analyzed to identify subtle changes in lesion morphology over time. A digital twin could incorporate these temporal patterns together with histopathological information and patient-level risk factors to estimate the probability of progression or additional melanoma development. This may facilitate personalized surveillance schedules rather than applying identical follow-up strategies to all patients.

Surgical planning is another important application. The digital twin could represent lesion location, depth, surrounding anatomical structures, and predicted margins. In selected cases, three-dimensional modeling could help clinicians

evaluate the potential effects of different surgical approaches on local control and cosmetic or functional outcomes. This may be particularly valuable for lesions located on the face, hands, feet, or other anatomically complex regions.

Advanced melanoma presents an even stronger rationale for dynamic digital twins. Modern management can involve immune checkpoint inhibitors, targeted therapy for selected molecular alterations, chemotherapy in specific settings, radiotherapy, surgery for selected metastatic lesions, and combinations or sequential strategies. Treatment responses vary substantially between individuals. A digital twin could incorporate tumor burden, molecular characteristics, immune features, treatment exposure, imaging response, circulating biomarkers, and adverse events to estimate the likely benefit of alternative treatment strategies.

Treatment resistance is an important challenge. A patient may initially respond to immunotherapy or targeted treatment and later develop progressive disease. A dynamic digital twin could update its predictions as new imaging or molecular data become available. Instead of simply recording that treatment has failed, the system could simulate alternative therapeutic pathways and estimate which options may provide the greatest probability of disease control.

Immunotherapy provides an especially relevant opportunity for digital twin development. Re-

sponse depends on complex interactions between tumor characteristics and the immune system. Future models may integrate tumor mutation profiles, immune-cell infiltration, inflammatory biomarkers, microbiological factors, and longitudinal treatment response to develop patient-specific representations of immune sensitivity. Such models could potentially identify patients most likely to benefit from immunotherapy and help anticipate immune-related toxicity.

Digital twins could also support long-term survivorship. Patients who achieve durable control may continue to experience treatment-related effects, psychological concerns, and risk of new primary tumors. A comprehensive digital twin could integrate surveillance findings, treatment history, patient-reported outcomes, and functional information to support individualized follow-up. This would extend the role of the technology beyond treatment selection and into long-term cancer management.

Digital Twins In Non-Melanoma Skin Cancers And Cutaneous Malignancies

Digital twins may also transform the management of non-melanoma skin cancers and other cutaneous malignancies. Basal cell carcinoma and cutaneous squamous cell carcinoma are common diseases, but their biological behavior

ranges from highly indolent lesions to locally destructive or metastatic tumors. A digital twin could help distinguish patients at low risk from those requiring more intensive management by integrating lesion characteristics, anatomical location, histopathology, previous recurrence, immune status, and treatment history.

For basal cell carcinoma, individualized modeling could support treatment selection among surgical excision, Mohs micrographic surgery, radiation, topical approaches, or systemic treatment in selected advanced cases. The digital twin could represent lesion dimensions, location, depth, recurrence history, and anatomical structures. This could help simulate the balance between achieving adequate tumor control and preserving cosmetic and functional outcomes.

Cutaneous squamous cell carcinoma provides additional opportunities because selected tumors have a meaningful risk of regional or distant spread. A digital twin could incorporate tumor thickness, differentiation, perineural invasion, lymphovascular invasion, anatomical location, immune status, and previous treatment. Serial imaging and clinical examination could update the predicted probability of recurrence or metastasis. This could support personalized surveillance and earlier intervention for high-risk patients.

Merkel cell carcinoma represents another important application because of its aggressive

biological behavior and substantial dependence on immune-related mechanisms. Digital twins could integrate pathology, imaging, immune biomarkers, and treatment response to estimate disease trajectory. As immunotherapy plays an increasingly important role in advanced disease, individualized simulation could potentially help identify treatment strategies that maximize benefit while minimizing toxicity.

Cutaneous lymphomas may also benefit from longitudinal digital modeling. Their clinical courses can be prolonged and heterogeneous, with patients undergoing repeated clinical examinations, biopsies, imaging, and systemic treatments. A digital twin could track lesion distribution, symptom burden, treatment exposure, and disease progression. Image-based monitoring may provide quantitative information about lesion changes and help distinguish treatment response from progression.

The integration of standardized clinical photography could be particularly valuable across these diseases. Patients can develop multiple lesions over large body areas, making longitudinal assessment challenging. Digital imaging systems can document lesion appearance and distribution over time. Artificial intelligence could identify new lesions, quantify changes in existing lesions, and integrate these observations into the digital twin.

Patient-centered outcomes are also important.

Skin cancers can produce pain, pruritus, bleeding, scarring, disfigurement, and functional impairment. A digital twin that focuses only on tumor control would fail to represent many outcomes that matter to patients. Incorporating symptom scores, photographs, patient-reported outcomes, and quality-of-life measures could help clinicians select treatments that balance oncological effectiveness with functional and cosmetic preservation.

For geographically dispersed patients, digital twins could potentially support remote monitoring. Standardized photographs and symptom assessments could be incorporated into a secure platform, allowing the computational model to identify changes that warrant in-person assessment. Such systems could be particularly useful for long-term surveillance, although clinical validation and appropriate safeguards would be essential before widespread implementation.

Digital Twins In Soft Tissue Sarcomas

Soft tissue sarcomas provide a particularly compelling setting for digital twin technology because of their substantial histological diversity, complex anatomical relationships, and frequent need for individualized multidisciplinary management. Sarcomas include many distinct subtypes with different molecular profiles, growth patterns, metastatic tendencies, and treatment

sensitivities. A conventional model based primarily on tumor size and stage may therefore fail to capture the complexity of individual disease behavior.

Magnetic resonance imaging is central to the evaluation of many soft tissue sarcomas. Digital twins could use serial magnetic resonance imaging to construct three-dimensional representations of tumor volume, location, internal structure, relationship with muscles and neurovascular structures, and response to treatment. These models could support surgical planning by helping clinicians visualize potential resection margins and the likely functional consequences of different approaches.

Radiotherapy planning represents another potential application. Patient-specific digital models could integrate tumor geometry with surrounding normal tissues and simulate different radiation strategies. The objective would be to maximize tumor control while minimizing exposure to healthy structures. For tumors located near major nerves, blood vessels, or critical organs, such simulation could be particularly valuable.

Neoadjuvant treatment provides an additional opportunity. Some patients receive chemotherapy or radiotherapy before surgery to reduce tumor burden or improve local control. Response can vary considerably between patients and sarcoma subtypes. A digital twin could integrate

serial imaging, pathology, molecular information, and treatment data to estimate whether a patient is responding adequately. This could potentially help determine whether the planned treatment course should be continued or modified.

Molecular profiling may also improve sarcoma digital twins. Certain sarcoma subtypes are associated with characteristic genomic alterations, while others demonstrate complex molecular patterns. Integrating these characteristics with imaging and pathological information could help identify biologically distinct disease trajectories. Artificial intelligence may detect relationships between molecular profiles and imaging phenotypes that are difficult to recognize using conventional methods.

Advanced and metastatic sarcoma represents another important application. Treatment may involve systemic chemotherapy, targeted agents, immunotherapy in selected settings, surgery for selected metastases, and radiotherapy. A digital twin could model the sequence and expected outcomes of these interventions. Because pulmonary metastases are common in several sarcoma subtypes, serial chest imaging could provide important information about treatment response and progression.

Functional outcomes should be incorporated into these models. Surgery for sarcoma can affect mobility, strength, pain, and limb function. A

treatment strategy that produces excellent local control but substantial functional impairment may not be optimal for every patient. Digital twins could therefore combine oncological outcomes with functional measures to support individualized treatment decisions.

Multidisciplinary tumor boards could benefit substantially from such systems. Surgeons, radiologists, pathologists, medical oncologists, radiation oncologists, and rehabilitation specialists could use a shared patient-specific computational representation. This could facilitate discussion of alternative strategies and improve coordination between different treatment modalities.

Artificial Intelligence, Imaging, And Multi-Omics Integration

The integration of artificial intelligence, imaging, computational pathology, and multi-omics is fundamental to the development of advanced digital twins in skin and soft tissue oncology. Skin cancers generate particularly rich visual data, including clinical photographs, dermoscopic images, total-body images, and microscopic pathology. Soft tissue cancers generate additional information from magnetic resonance imaging, computed tomography, positron emission tomography, and other modalities. Artificial intelligence provides tools for transforming these heterogeneous data into quantitative

features.

Deep learning can analyze dermatological images and identify patterns associated with malignant lesions. When repeated images are available, models can also evaluate temporal changes. Rather than assessing an image independently, a digital twin could compare lesion characteristics across multiple time points and determine whether the observed trajectory is consistent with benign stability, treatment response, recurrence, or progression.

Radiomics can provide quantitative information from cross-sectional imaging. Features describing tumor heterogeneity, shape, texture, and spatial relationships may contribute to individualized prediction. In soft tissue sarcomas, radiomic characteristics may potentially help distinguish tumor subtypes, estimate treatment response, and predict recurrence or metastatic behavior. These features can become part of the evolving digital representation.

Computational pathology can complement imaging. Whole-slide images can reveal cellular and tissue-level characteristics that may not be visible clinically. Artificial intelligence can quantify tumor morphology, stromal architecture, necrosis, immune infiltration, and other features. Integrating pathology with imaging may allow digital twins to connect macroscopic tumor behavior with microscopic biology.

Multi-omics information can provide additional

depth. Genomics can characterize mutations and structural alterations, transcriptomics can describe gene-expression patterns, proteomics can identify protein-level changes, and metabolomics can reflect cellular metabolic activity. These data may help explain why apparently similar tumors behave differently and why patients respond differently to the same treatment.

Artificial intelligence can integrate these modalities using multimodal architectures. Instead of analyzing each data source independently, multimodal models can learn relationships among imaging, pathology, molecular characteristics, clinical variables, and longitudinal outcomes. The resulting representation may provide a more complete model of individual disease biology.

However, multimodal integration creates substantial challenges. Different data sources have different scales, formats, acquisition protocols, and levels of reliability. Missing data are common, particularly in rare cancers where extensive molecular profiling may not be available for every patient. Models must therefore be designed to accommodate incomplete information and communicate uncertainty.

External validation is essential. An imaging model trained on photographs acquired using one camera system may perform differently when images are obtained under different lighting or technical conditions. Similarly, pathology models may be affected by differences in staining

procedures and slide scanners. Sarcoma imaging models may be influenced by differences in magnetic resonance protocols. Digital twins must therefore undergo rigorous validation across institutions, technologies, and patient populations.

Explainability should also be prioritized. Clinicians need to know why a digital twin predicts a particular outcome. Visual highlighting of relevant imaging or pathology features, contribution analysis for clinical variables, and uncertainty estimates may improve transparency. The objective is not simply to produce a highly accurate algorithm but to create a clinically useful system that can be understood, questioned, and appropriately integrated into professional decision-making.

Adaptive Treatment And Personalized Clinical Decision-Making

Digital twins could fundamentally change the management of skin and soft tissue cancers by enabling adaptive treatment based on continuously updated information. Conventional treatment planning is often performed at diagnosis, with subsequent changes made when clear evidence of progression or toxicity emerges. A digital twin could instead continuously estimate the patient's current disease state and simulate alternative strategies as new information becomes available.

In melanoma, adaptive treatment could incorporate serial imaging, circulating biomarkers, molecular testing, treatment response, and immune-related adverse events. If a patient demonstrates a strong response to immunotherapy, the digital twin could update the expected benefits of continuing treatment. If progression develops, new molecular or imaging information could be incorporated to estimate alternative strategies. This could potentially reduce delays in changing ineffective therapy.

In soft tissue sarcomas, adaptive treatment may involve serial magnetic resonance imaging and functional assessment during neoadjuvant treatment. Changes in tumor volume and internal characteristics could update the digital twin and influence estimates of surgical feasibility. Functional information could also help clinicians evaluate whether a planned procedure is likely to preserve meaningful mobility and quality of life.

Surgical decision-making may benefit from patient-specific simulation. A digital twin could represent tumor anatomy and surrounding structures while modeling potential resection approaches. Surgeons could compare alternative strategies in terms of margins, functional consequences, reconstruction requirements, and expected recovery. Although such simulations would not replace surgical expertise, they could provide an additional layer of quantitative information.

Treatment personalization should also incorporate patient preferences. The importance of cosmetic appearance, limb function, pain control, treatment duration, risk of recurrence, and adverse effects varies among individuals. Digital twins could allow clinicians to compare treatment strategies according to outcomes that are specifically meaningful to each patient.

Surveillance is another important area. Patients with melanoma, high-risk cutaneous squamous cell carcinoma, sarcoma, and other malignancies may require long-term monitoring. A digital twin could estimate individualized recurrence risk using treatment history, tumor biology, imaging, pathology, and longitudinal observations. Surveillance schedules could potentially become more dynamic, with intensified follow-up for patients whose predicted risk increases.

Patient-reported outcomes can make these systems more comprehensive. Symptoms such as pain, fatigue, pruritus, functional limitations, anxiety, and body-image concerns can be incorporated into the computational representation. This creates a broader definition of treatment success that includes not only tumor control but also the patient's lived experience.

The clinical value of adaptive digital twins will ultimately depend on prospective validation. A prediction that appears accurate retrospectively may not necessarily improve treatment out-

comes when incorporated into clinical practice. Trials should determine whether digital twin-guided decisions improve survival, recurrence control, toxicity, function, quality of life, and patient satisfaction. Integration into multidisciplinary workflows will also be essential for ensuring that computational recommendations are interpreted appropriately.

Challenges, Ethical Considerations, And Clinical Validation

Despite their promise, digital twins for skin and soft tissue cancers face significant challenges. Data quality is one of the most fundamental. Clinical records may contain missing information, inconsistent terminology, and incomplete treatment histories. Imaging can vary according to equipment and acquisition protocols, while dermatological photographs may differ in lighting, focus, distance, and skin background. Pathology can also vary according to tissue preparation, staining, and interpretation. These differences can influence artificial intelligence performance.

Generalizability is particularly important in dermatological applications. Skin appearance and imaging characteristics can vary across populations, and algorithms trained predominantly on one group may perform less accurately in underrepresented populations. Digital twins should therefore be evaluated across diverse patient groups and a wide range of disease presentations.

Bias can also arise from differences in healthcare access. Patients who receive extensive molecular testing, advanced imaging, or repeated specialist evaluation may be better represented in training datasets than patients treated in resource-limited settings. Models based on such data may inadvertently encode healthcare inequalities. Developers should therefore examine model performance across different healthcare environments and consider strategies for robust prediction when data are incomplete.

Privacy is another major concern. Skin and facial photographs may contain identifiable information, while genomic and pathology data can be highly sensitive. Secure storage, encryption, controlled access, appropriate consent, and responsible data governance are essential. Patients should understand how their images and biological information are used in digital twin development.

The ethical use of artificial intelligence also requires transparency. A digital twin should not present uncertain predictions as definitive conclusions. Clinicians must be able to understand the limitations of the model and identify circumstances in which it should not be trusted. Human oversight is particularly important when treatment decisions involve major surgery, permanent functional consequences, or poten-

tially life-threatening toxicity.

Continuous learning presents regulatory challenges. A digital twin that changes as new data are incorporated may not remain identical to the system initially validated. Mechanisms for monitoring model performance, documenting updates, recalibrating predictions, and detecting unexpected changes will therefore be necessary.

Clinical validation should focus on meaningful outcomes rather than technical metrics alone. Studies should evaluate whether digital twin-guided care improves local control, recurrence-free survival, metastatic outcomes, overall survival, treatment toxicity, functional recovery, cosmetic outcomes, and quality of life. For rare sarcomas and uncommon cutaneous cancers, international multicenter collaboration may be necessary to obtain sufficient sample sizes.

Cost-effectiveness is also important. Digital twin systems may require substantial investments in imaging infrastructure, data integration, computational resources, cybersecurity, and specialized personnel. Their adoption will therefore depend not only on technological feasibility but also on evidence that they provide sufficient clinical value to justify these costs.

Future Perspectives And Conclusion

The future of digital twins in skin and soft tissue oncology is likely to involve increas-

ingly sophisticated integration of clinical photographs, dermoscopy, whole-body imaging, radiology, pathology, genomics, transcriptomics, treatment histories, wearable technologies, and patient-reported outcomes. As computational methods improve, the digital twin may evolve from a predictive model into a comprehensive representation of tumor biology and the patient's physiological and functional state.

One promising direction is the integration of mechanistic models with artificial intelligence. Machine learning can identify patterns within large datasets, while mechanistic models can represent biological processes such as tumor growth, metastatic spread, immune response, and treatment resistance. Hybrid models may therefore provide predictions that are both powerful and biologically interpretable.

Real-time monitoring could further enhance digital twins. Repeated clinical photographs, remote symptom assessments, wearable devices, and home-based measurements may allow continuous observation of patients during treatment and surveillance. For selected skin cancers, changes in lesion appearance could potentially be detected earlier. For sarcoma patients, changes in symptoms or functional status could complement periodic imaging.

Three-dimensional and spatial modeling may also become increasingly important. Digital twins could represent tumors and surrounding

anatomical structures in three dimensions, allowing clinicians to simulate surgery, radiation treatment, reconstruction, and other interventions. This may be particularly valuable for complex sarcomas and tumors located near critical structures.

Digital twins may also support virtual treatment experimentation. Multiple therapeutic scenarios could be simulated before treatment is delivered, providing individualized estimates of potential benefits and risks. Although such simulations cannot replace prospective clinical evidence, they could help clinicians prioritize options and identify patients who may benefit from particular strategies.

The technology may have particular importance in rare cancers. Soft tissue sarcomas and uncommon cutaneous malignancies often have limited evidence because individual histological subtypes are relatively rare. Digital twins could integrate multicenter and international data to improve individualized prediction while simultaneously supporting research into disease mechanisms and treatment response.

Patient-centered care should remain the central objective. The most successful digital twins will not simply maximize predictive accuracy. They will integrate oncological outcomes with functional status, cosmetic considerations, symptoms, treatment burden, and patient preferences. Such systems could help clinicians and

patients evaluate treatment options according to the outcomes that matter most to the individual.

In conclusion, digital twins represent a promising next-generation framework for the treatment of skin and soft tissue cancers. Their ability to integrate clinical, imaging, pathological, molecular, and longitudinal information could provide a dynamic representation of individual disease and facilitate simulation of alternative treatment strategies. Potential applications extend from early detection and surveillance to surgical planning, systemic treatment selection, adaptive therapy, recurrence monitoring, and long-term survivorship.

The most important transformation may be the shift from static treatment planning toward continuously personalized cancer management. As new information becomes available, the digital twin could update its representation and provide revised estimates of disease trajectory and treatment response. If challenges involving data quality, bias, privacy, interoperability, interpretability, regulation, and clinical validation are adequately addressed, digital twins could become an important component of precision oncology. Their integration into multidisciplinary care may ultimately enable treatment strategies that are not only more biologically precise but also more adaptive, functional, and responsive to the individual needs of patients with skin and soft tissue cancers.

9. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN HEAD AND NECK CANCERS

Background

Head and neck cancers comprise a heterogeneous group of malignancies arising from the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, salivary glands, nasal cavity, paranasal sinuses, and other structures of the upper aerodigestive tract. Most are squamous cell carcinomas, although several other histological malignancies can occur. These cancers represent a major global health burden and can produce substantial mortality and long-term functional impairment. Their clinical management is particularly complex because tumors develop in anatomical regions responsible for essential functions such as breathing, swallowing, speech, taste, hearing, and facial expression. Consequently, successful treatment requires not only effective tumor control but also preservation of function, appearance, and quality of life.

Although substantial advances have been achieved in surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, endoscopy, molecular diagnostics, and reconstructive techniques, treatment selection remains challenging. Patients with apparently similar tumor

stages may experience different responses to the same treatment. Human papillomavirus status, smoking and alcohol exposure, tumor biology, anatomical location, immune characteristics, molecular alterations, nutritional status, and comorbidities can all influence outcomes. Furthermore, head and neck cancers may recur locally or regionally, develop distant metastases, or produce severe treatment-related complications.

Digital twin technology represents a promising next-generation approach to these challenges. A digital twin is a dynamic computational representation of an individual patient that integrates clinical, anatomical, imaging, pathological, molecular, and longitudinal information. Unlike conventional prediction models that generally provide a fixed estimate based on baseline characteristics, a digital twin can potentially evolve as new information becomes available. In head and neck oncology, the digital twin could incorporate endoscopic findings, computed tomography, magnetic resonance imaging, positron emission tomography, pathology, genomic profiles, treatment exposure, functional assessments, and patient-reported outcomes.

Artificial intelligence can provide the computational foundation for transforming these heterogeneous data into individualized predictions. Deep learning can analyze medical images and digital pathology, natural language processing can extract information from clinical records,

and machine learning can integrate multiple predictors into treatment-response models. A digital twin could potentially simulate alternative treatment pathways and estimate their likely consequences before therapy is delivered.

This approach may be particularly valuable because head and neck cancer treatment frequently involves multidisciplinary decisions. Surgery, radiotherapy, systemic therapy, dental care, nutrition, speech and swallowing rehabilitation, and reconstructive procedures may all contribute to management. Digital twins could provide a shared patient-specific representation that helps multidisciplinary teams compare treatment strategies.

The ultimate objective is not to replace clinical judgment but to support more precise and adaptive decision-making. As treatment progresses, new imaging, pathology, biomarkers, functional assessments, and patient-reported outcomes could update the digital twin. This could allow clinicians to recognize treatment resistance earlier, adjust treatment intensity, anticipate complications, and balance tumor control with preservation of important functions. If appropriately validated, digital twins could therefore contribute to a new model of head and neck cancer care in which treatment continuously adapts to the evolving characteristics of each patient.

Digital Twin Architecture For

Head And Neck Cancer Care

A digital twin for head and neck cancer requires an architecture capable of integrating highly diverse information across anatomical, biological, functional, and temporal dimensions. The first component is the clinical data layer. This layer may include age, sex, smoking and alcohol exposure, human papillomavirus status, comorbidities, medications, performance status, nutritional condition, dental status, previous cancer treatment, and other patient characteristics. These variables can influence treatment tolerance, complications, recurrence, and survival and therefore need to be incorporated into the computational representation.

The second component is anatomical and imaging information. Head and neck tumors are particularly dependent on precise anatomical assessment because small differences in tumor location can influence surgical accessibility, radiation exposure, functional outcomes, and prognosis. Computed tomography can provide information about bone involvement, lymph nodes, and anatomical extension, while magnetic resonance imaging offers detailed soft tissue characterization. Positron emission tomography can provide metabolic information and assist in staging and treatment-response assessment. Endoscopic imaging provides direct visualization of mucosal lesions and can be repeatedly incorporated into a longitudinal model.

Three-dimensional reconstruction is an important potential feature of the digital twin. Imaging data could be converted into patient-specific anatomical models representing the tumor, lymph nodes, airway, vascular structures, nerves, salivary glands, muscles, and other critical tissues. Such models could support treatment simulation and surgical planning. In radiotherapy, they could help visualize the relationship between tumor targets and organs at risk. In surgery, they could assist evaluation of resection approaches and reconstructive strategies.

Pathology represents another essential layer. Histological type, tumor grade, depth of invasion, perineural invasion, lymphovascular invasion, extranodal extension, surgical margins, and other pathological characteristics provide important prognostic information. Digital pathology and artificial intelligence may allow additional morphological features to be extracted from whole-slide images.

Molecular information can further characterize tumor biology. Human papillomavirus status is particularly important in oropharyngeal cancer, while genomic alterations, immune-related biomarkers, gene expression patterns, and other molecular characteristics may contribute to individualized treatment selection. These data could be incorporated into the digital twin to improve predictions of treatment response and recurrence.

The artificial intelligence layer can integrate these different data types. Machine learning can analyze structured clinical variables, deep learning can process images and pathology, and natural language processing can extract information from electronic health records. Longitudinal modeling can then update predictions as the patient's condition changes.

Finally, the simulation layer can compare alternative treatment strategies. Possible outcomes include local control, regional recurrence, distant metastasis, overall survival, treatment toxicity, swallowing function, speech, nutritional status, xerostomia, pain, and quality of life. A useful digital twin should also provide uncertainty estimates and indicate which variables most strongly influence its predictions. This architecture would allow the technology to function as an integrated decision-support platform rather than simply another isolated predictive algorithm.

Digital Twins In Oral Cavity And Oropharyngeal Cancers

Oral cavity and oropharyngeal cancers provide important opportunities for digital twin applications because treatment frequently requires careful consideration of tumor anatomy, lymphatic spread, human papillomavirus status, and functional outcomes. Oral squamous cell carcinoma may involve the tongue, floor of the

mouth, gingiva, buccal mucosa, hard palate, or other structures. Tumor location and depth can influence surgical planning, nodal management, reconstruction, and prognosis. A patient-specific digital twin could integrate clinical examination, endoscopic findings, magnetic resonance imaging, computed tomography, pathology, and molecular information to construct a detailed representation of disease.

Surgical planning could be one of the earliest applications. Three-dimensional models could represent the tumor and surrounding structures and allow clinicians to simulate alternative resection strategies. The model could incorporate expected surgical margins, nearby nerves and vessels, and potential reconstruction requirements. This may help multidisciplinary teams evaluate the likely balance between oncological control and functional preservation.

Lymph-node management is another important area. Head and neck cancers can spread through complex lymphatic pathways, and the risk of occult nodal disease varies according to tumor characteristics. A digital twin could integrate tumor depth, location, imaging findings, pathological features, and molecular information to estimate individualized nodal risk. This could potentially support decisions regarding elective neck treatment and surveillance.

Oropharyngeal cancer presents additional opportunities because human papillomavirus sta-

tus is strongly relevant to prognosis and treatment considerations. Digital twins could integrate viral status with imaging, pathology, smoking history, tumor stage, and treatment response. For patients receiving radiotherapy or chemoradiotherapy, serial imaging and clinical data could update the computational model and provide individualized estimates of treatment response.

Treatment de-escalation represents an area where digital twins could potentially contribute to research and future clinical practice. Selected patients with favorable biological characteristics may have different risk profiles from patients with more aggressive disease. A digital twin could simulate the predicted consequences of alternative treatment intensities and help identify patients for whom reduced treatment burden might be investigated. Such decisions would require prospective validation and should not be based solely on retrospective computational predictions.

Functional outcomes are particularly important in oral and oropharyngeal cancers. Treatment can affect swallowing, speech, chewing, taste, saliva production, and nutritional status. A digital twin could incorporate baseline and longitudinal functional assessments to predict these outcomes under different treatment strategies. This would enable treatment planning to consider not only whether a patient is likely to sur-

vive but also how treatment may affect daily life. Long-term surveillance could also become more individualized. Clinical photographs, endoscopic examinations, imaging, symptoms, and patient-reported outcomes could be incorporated into the digital twin. Changes that increase the predicted probability of recurrence could trigger additional assessment, while stable low-risk trajectories might support more individualized follow-up. Such systems could potentially improve early detection of recurrence while reducing unnecessary procedures.

Digital Twins In Laryngeal, Hypopharyngeal, And Nasopharyngeal Cancers

Laryngeal, hypopharyngeal, and nasopharyngeal cancers present distinct challenges that may be addressed through patient-specific digital modeling. Laryngeal cancers are particularly important because treatment decisions must balance oncological control with preservation of voice, swallowing, and airway function. Depending on tumor stage and location, treatment may involve endoscopic surgery, partial or total laryngectomy, radiotherapy, chemotherapy, or combined approaches. A digital twin could simulate the potential consequences of these strategies for an individual patient.

Three-dimensional anatomical modeling could be particularly valuable in laryngeal cancer. Imaging and endoscopic information could be combined to represent the tumor, vocal cords, airway, cartilage, and surrounding structures. This model could support evaluation of surgical approaches and radiation plans. Functional modeling could incorporate predicted effects on voice and swallowing, allowing treatment options to be compared according to both tumor control and functional preservation.

Organ preservation strategies are another important area. For selected patients, chemoradiotherapy may provide an alternative to total laryngectomy. However, preserving the larynx anatomically does not always guarantee satisfactory function. Some patients may experience chronic aspiration, swallowing dysfunction, airway complications, or severe voice impairment. A digital twin could potentially integrate baseline functional characteristics, imaging, tumor biology, and treatment response to estimate the probability of meaningful functional preservation.

Hypopharyngeal cancers often present at advanced stages and may require extensive multimodal treatment. Their anatomical location can make surgery complex, while treatment may substantially affect swallowing and nutritional status. A digital twin could represent tumor extent, lymph-node involvement, nutritional status, and treatment response to compare alternative management pathways. Serial imaging

during therapy could update predictions and potentially identify patients who are not responding adequately.

Nasopharyngeal cancer presents another distinctive setting because of its anatomical location and biological characteristics. Radiotherapy and systemic treatment play major roles, while advanced imaging and molecular information can support staging and response assessment. A digital twin could integrate magnetic resonance imaging, positron emission tomography, pathology, viral biomarkers where relevant, treatment exposure, and longitudinal outcomes. This could facilitate individualized estimation of response and recurrence risk.

Radiotherapy optimization may be especially valuable across these cancers. Head and neck radiation planning requires precise targeting while minimizing exposure to organs such as the salivary glands, spinal cord, brainstem, optic structures, swallowing muscles, and other critical tissues. A patient-specific digital twin could model tumor geometry and normal tissue anatomy and simulate alternative treatment plans. Artificial intelligence could help identify plans that optimize the balance between tumor control and expected toxicity.

Adaptive radiotherapy represents a natural extension of this concept. Tumors can change in size during treatment, while patients may lose weight or experience anatomical changes. A

digital twin could incorporate repeated imaging and physiological information to update the patient's anatomical representation. Treatment plans could then potentially be adapted according to the evolving geometry. This could improve target coverage and reduce unnecessary radiation exposure to normal tissues.

Digital Twins In Salivary Gland And Other Head And Neck Malignancies

Salivary gland malignancies provide another important application for digital twins because they include numerous histological subtypes with substantially different biological behavior. Tumors may arise in the parotid, submandibular, sublingual, or minor salivary glands and can vary in aggressiveness, perineural spread, recurrence patterns, and treatment sensitivity. Conventional staging alone may therefore provide an incomplete representation of prognosis.

A digital twin could integrate imaging, pathology, molecular characteristics, and clinical information to estimate individualized disease trajectories. Magnetic resonance imaging is particularly important for assessing soft tissue extension and perineural spread. A patient-specific computational model could represent the tumor and its relationship with facial nerves, major vessels, muscles, and other structures. This could support surgical planning and help

anticipate the potential functional consequences of resection.

Perineural invasion is especially relevant in several head and neck cancers. Tumor spread along nerves can influence surgical margins, radiation planning, recurrence risk, and neurological outcomes. Digital twins could integrate imaging and pathology to model potential pathways of perineural extension. Such representations could support multidisciplinary treatment planning and potentially identify patients requiring more intensive local therapy.

For rare salivary gland tumors, molecular profiling may be particularly valuable. Different histological subtypes may contain characteristic molecular alterations that influence diagnosis and treatment. Integrating molecular information into a digital twin could help explain differences in tumor behavior and identify potential therapeutic opportunities.

The technology may also support treatment planning for advanced disease. Patients with recurrent or metastatic salivary gland cancers may undergo surgery, radiation, systemic therapy, targeted treatment, or combinations. Because evidence for rare tumors can be limited, individualized computational simulation may provide useful supplementary information when clinicians evaluate complex treatment options.

Cutaneous head and neck malignancies can also be integrated into broader digital twin systems.

Tumors involving the scalp, face, ear, nose, or other exposed anatomical regions may create unique challenges involving cosmetic and functional preservation. Standardized photography, dermoscopy, imaging, pathology, and patient-reported outcomes could be combined to create a comprehensive representation of disease and treatment effects.

Quality of life should remain central. Head and neck treatments can affect facial appearance, hearing, speech, swallowing, saliva production, taste, nutrition, and psychological well-being. A digital twin that evaluates only survival may therefore produce an incomplete treatment recommendation. Incorporating functional and patient-reported outcomes would allow clinicians to evaluate treatment strategies from a broader perspective.

Longitudinal survivorship is another potential application. Patients who remain disease-free may continue to require rehabilitation, nutritional support, dental care, speech therapy, swallowing therapy, and monitoring for late treatment effects. A digital twin could integrate these data with recurrence risk and provide a dynamic representation of long-term health. This could support personalized survivorship care rather than focusing exclusively on tumor surveillance.

Artificial Intelligence, Imaging, And Multi-Omics Integration

Artificial intelligence provides the technological foundation for integrating the complex data required by head and neck cancer digital twins. These patients generate information from clinical examination, endoscopy, computed tomography, magnetic resonance imaging, positron emission tomography, pathology, laboratory testing, molecular profiling, treatment records, and functional assessments. Each modality captures a different aspect of disease, and multimodal artificial intelligence can potentially combine them into a unified patient representation.

Radiomics can extract quantitative information from medical imaging that may not be apparent through conventional visual interpretation. Tumor texture, shape, intensity, heterogeneity, metabolic characteristics, and spatial relationships may provide information about tumor aggressiveness and treatment response. Deep learning can identify complex imaging features associated with recurrence, metastatic disease, or treatment sensitivity.

Computational pathology provides complementary microscopic information. Artificial intelligence can analyze digitized pathology slides and identify tumor architecture, cellular morphology, stromal characteristics, immune infiltration, necrosis, and other features. These characteristics may contribute to prediction of recurrence or treatment response. Combining pathology with radiomics could connect microscopic biology with macroscopic tumor behavior.

Human papillomavirus and other biological markers can be incorporated into multimodal models. For oropharyngeal cancers, viral status can be combined with smoking history, imaging, pathology, and treatment response. Other head and neck tumors may benefit from genomic, transcriptomic, proteomic, or immune-related data. Multi-omics integration can help distinguish biologically different tumors that appear similar based on conventional staging.

Natural language processing can also contribute substantially. Clinical information is frequently contained in unstructured notes, pathology reports, radiology reports, operative documentation, and multidisciplinary tumor board records. Natural language processing can convert these sources into structured variables that become part of the digital twin.

Longitudinal modeling is essential because head and neck cancers and their treatment effects evolve over time. Serial imaging can reveal tumor response or progression, while repeated functional assessments can document changes in swallowing, speech, nutrition, and quality of life. A digital twin can incorporate these observations and update its predictions continuously.

However, multimodal systems face significant technical challenges. Imaging protocols differ between institutions, pathology slides may be

processed differently, molecular testing may not be uniformly available, and clinical documentation varies considerably. Missing data are common. Artificial intelligence models therefore need robust strategies for incomplete and heterogeneous information.

External validation is critical. A model trained in one institution may not generalize to other populations or imaging systems. This is especially important in head and neck cancer because disease prevalence, treatment practices, and patient characteristics vary across regions. Multicenter validation should therefore be considered a fundamental requirement.

Interpretability is equally important. Clinicians should understand the main factors driving a digital twin's prediction and the degree of uncertainty associated with each estimate. Explainable artificial intelligence, visualization of relevant anatomical regions, feature attribution, and uncertainty quantification can help clinicians assess whether the computational output is clinically plausible.

Adaptive Treatment And Personalized Clinical Decision-Making

The dynamic nature of digital twins creates the possibility of adaptive treatment throughout the head and neck cancer journey. Instead of selecting a fixed treatment strategy based primarily on initial staging, clinicians could continuously

update the computational representation using new imaging, pathology, biomarkers, treatment responses, and functional information.

Adaptive radiotherapy is a particularly important application. During a course of radiation, tumor volume can change, while weight loss and tissue changes can alter anatomy. These changes may affect the relationship between the target and organs at risk. A digital twin could incorporate repeated imaging to update the anatomical representation and support adaptive treatment planning. Artificial intelligence could help identify clinically meaningful changes and estimate whether a revised treatment plan would improve the balance between tumor control and toxicity.

Systemic treatment can also be adapted. Patients receiving chemotherapy, targeted therapy, or immunotherapy may demonstrate substantial differences in response. A digital twin could integrate imaging, biomarkers, adverse events, and clinical status to estimate whether continuing the current treatment remains beneficial. If the predicted probability of response declines, alternative strategies could be simulated.

Surgical planning can similarly benefit from adaptive modeling. Tumor anatomy may change after neoadjuvant treatment, and updated imaging could modify the predicted feasibility of organ-preserving surgery or reconstructive approaches. A digital twin could therefore support multidisciplinary reassessment immediately be-

fore definitive treatment.

Functional outcomes should be included throughout this process. A patient receiving treatment for laryngeal cancer, for example, may prioritize preservation of voice and swallowing. Another patient may prioritize maximal tumor control even if treatment carries greater functional risks. Digital twins could incorporate these preferences and estimate treatment outcomes according to individualized priorities.

Patient-reported outcomes could include swallowing difficulty, speech impairment, pain, xerostomia, fatigue, taste changes, nutritional status, psychological distress, and social functioning. Combining these data with oncological measures would allow treatment decisions to reflect the full consequences of therapy.

Surveillance could also become personalized. Recurrence risk could be continuously estimated using tumor biology, treatment response, imaging, symptoms, and molecular information. Patients with increasing predicted risk might undergo more intensive assessment, while stable low-risk patients could potentially follow less intensive surveillance schedules. Such approaches could reduce unnecessary procedures while maintaining appropriate monitoring.

Digital twins could further support multidisciplinary tumor boards by providing a common computational representation of the patient. Surgeons, radiation oncologists, medical

oncologists, radiologists, pathologists, speech and swallowing specialists, nutritionists, and rehabilitation professionals could examine predicted consequences of alternative treatment strategies. This could improve communication and facilitate more coordinated decisions.

However, adaptive digital twins should remain under clinical supervision. Algorithmic predictions can be affected by missing information, model uncertainty, and unexpected biological changes. The appropriate role of the technology is to support clinical reasoning rather than replace it. Prospective studies are necessary to determine whether these systems actually improve treatment outcomes and patient experience.

Challenges, Ethical Considerations, And Clinical Validation

The implementation of digital twins in head and neck oncology presents substantial challenges related to data quality, model performance, privacy, bias, clinical workflow, and regulation. One of the most important issues is the heterogeneity of clinical data. Imaging protocols, pathology techniques, endoscopic equipment, laboratory measurements, and documentation practices can differ considerably between institutions. These differences may affect the performance of artificial intelligence systems.

Generalizability is particularly important because head and neck cancer populations vary

in risk factors, tumor biology, treatment practices, and healthcare access. A model developed using data from one institution may not perform equally well elsewhere. External validation across multiple institutions and populations should therefore be required before clinical implementation.

Bias can occur when training datasets underrepresent particular patient groups. This can produce unequal prediction accuracy and potentially influence treatment recommendations. Digital twin developers should evaluate performance across relevant demographic, clinical, and biological subgroups. The use of diverse multicenter datasets can reduce some of these risks.

Privacy is another major concern. Digital twins may contain facial photographs, voice recordings, imaging, genomic data, pathology, and detailed treatment histories. Some of these data are inherently identifiable. Secure storage, encryption, controlled access, appropriate consent, and strict governance mechanisms are therefore essential.

The use of facial and voice data raises additional considerations because these characteristics can potentially identify patients even after conventional de-identification. Systems must therefore apply strong safeguards when storing and processing these data. Patients should receive clear information about how their data are used for

clinical care, research, and model development.

Responsibility for clinical decisions must also remain clear. If a digital twin recommends one treatment strategy and an adverse outcome occurs, clinicians and institutions need defined frameworks for accountability. Digital twins should provide uncertainty estimates and allow clinicians to override recommendations when clinical judgment indicates that the model may be inappropriate.

Continuous learning creates regulatory complexity. A digital twin may change as new information is incorporated, meaning that its behavior can evolve after deployment. Systems therefore require continuous performance monitoring, documentation of model updates, recalibration procedures, and mechanisms for identifying performance deterioration.

Clinical validation should focus on outcomes that matter to patients. Technical measures such as discrimination and calibration are important, but they do not demonstrate clinical benefit. Prospective studies should evaluate survival, recurrence, treatment toxicity, swallowing, speech, nutritional outcomes, quality of life, and patient satisfaction. The effect on healthcare utilization and treatment costs should also be assessed.

Implementation research will be essential. A technically sophisticated digital twin may fail to improve care if it is difficult to integrate into clinical workflows. Interfaces should be de-

signed around the needs of clinicians and multidisciplinary teams. The system should present relevant information clearly without creating excessive alert burden or requiring unnecessary data entry.

Ultimately, successful implementation will require collaboration among clinicians, data scientists, engineers, statisticians, patients, ethicists, and policymakers. Digital twins should be developed as clinically grounded technologies rather than purely computational projects.

Future Perspectives And Conclusion

The future of digital twins in head and neck oncology is likely to involve increasingly comprehensive integration of anatomical, biological, functional, and patient-centered information. Clinical photographs, endoscopic images, computed tomography, magnetic resonance imaging, positron emission tomography, digital pathology, genomic data, treatment records, wearable technologies, and patient-reported outcomes could eventually contribute to a continuously evolving patient-specific model.

One important future direction is the integration of mechanistic biological models with artificial intelligence. Data-driven models can identify complex patterns, while mechanistic models can represent tumor growth, metastatic spread, immune response, and treatment effects. Combining these approaches may improve both predictive performance and interpretability.

Three-dimensional digital twins may become increasingly important for surgical and radiation planning. Patient-specific models could represent tumors, lymph nodes, nerves, blood vessels, muscles, glands, and other structures. Clinicians could simulate alternative treatment strategies and visualize their potential effects. This may be particularly useful for complex tumors involving the skull base, larynx, oral cavity, or major neurovascular structures.

Real-time monitoring could also transform survivorship and treatment management. Repeated symptom reporting, swallowing assessments, nutritional measurements, voice analysis, and wearable data could provide continuous information about patient status. These observations could be incorporated into the digital twin to detect deterioration earlier and guide supportive care.

The integration of digital twins with precision immuno-oncology may be especially promising. Future models may combine tumor genomics, immune-cell characteristics, imaging phenotypes, treatment history, and longitudinal biomarkers to simulate immune responses. This could support more individualized selection and sequencing of immunotherapies.

Digital twins could also facilitate virtual treatment experimentation. Multiple treatment path-

ways could be simulated before clinical intervention, allowing multidisciplinary teams to compare predicted tumor control, toxicity, functional outcomes, and quality of life. These simulations would not replace clinical trials, but they could support hypothesis generation and individualized treatment planning.

Patient-centered outcomes should remain a core component of future systems. Head and neck cancer treatment can profoundly affect identity, communication, nutrition, social interaction, and daily functioning. A digital twin that incorporates only survival and recurrence would therefore provide an incomplete representation of treatment success. Future models should explicitly incorporate speech, swallowing, appearance, nutritional status, psychological well-being, and patient preferences.

In conclusion, digital twins represent a promising next-generation framework for the treatment of head and neck cancers. Their ability to integrate clinical characteristics, imaging, pathology, molecular information, treatment exposure, functional outcomes, and longitudinal data could create a dynamic representation of each patient's disease. Potential applications extend from diagnosis and risk assessment to surgical planning, adaptive radiotherapy, systemic treatment selection, surveillance, rehabilitation, and survivorship care.

The most important potential transformation

is the transition from static, population-based treatment planning toward continuously personalized management. As the patient's disease and functional status change, the digital twin could update its predictions and support new treatment decisions. If challenges related to data quality, bias, privacy, interoperability, interpretability, regulation, and prospective clinical validation are successfully addressed, digital twins could become an important component of precision head and neck oncology. Their integration into multidisciplinary practice may ultimately enable treatment strategies that are more adaptive, biologically informed, function-preserving, and aligned with the individual priorities of patients.

10. NEXT-GENERATION CANCER TREATMENT USING DIGITAL TWINS IN OTHER CANCERS

Next-Generation Cancer Treatment Using Digital Twins in Ovarian Tumors

Ovarian cancer remains the most lethal gynecological malignancy, primarily because the vast majority of cases are diagnosed at an advanced stage. The current standard of care relies on aggressive cytoreductive surgery combined with platinum-based systemic chemotherapy, typically paclitaxel and carboplatin. However, clinical responses vary among patients, highlighting an urgent need for predictive tools capable of capturing these divergent outcomes. Traditional experimental platforms, such as two-dimensional in vitro cultures and animal models, frequently fail to replicate long-term treatment courses, the intricate three-dimensional architecture of the tumor microenvironment, or the dynamic complexities of tumor-drug interactions. To bridge this gap, the integration of Digital Twin (DT) technology with artificial intelligence (AI) and machine learning (ML) has emerged as a revolutionary frontier in oncology. A Digital Twin acts as a dynamic, virtual counterpart of a patient's specific pathology. By continuously consolidat-

ing vast streams of multi-omic data, including genetic profiles, clinical imaging, and environmental factors, DTs provide a holistic, real-time simulation of disease progression.

In clinical practice, these predictive models offer several transformative advantages:

• Early detection and risk stratification: Identifying malignant shifts before they manifest macroscopically.
• Adaptive therapeutic customization: Allowing oncologists to simulate and forecast patient-specific reactions to diverse therapeutic interventions.

• Protocol optimization: Modeling the precise kinetics of chemotherapy or radiotherapy regimens to maximize cytotoxicity within the tumor while minimizing systemic toxicity.

• Survival optimization: Aligning adaptive therapies directly with evolving tumor behaviors to ultimately improve long-term patient survival.

A prime example of this technology in action is the development of high-performance, GPU-accelerated (Graphics Processing Unit) digital twin frameworks, which have unlocked the ability to simulate chemotherapy dynamics at cellular resolution. Notably, Chen et al. developed OVTwin, a pioneering GPU-accelerated digital twin framework designed to simulate drug diffusion, cellular uptake, and subsequent cell fate

within three-dimensional ovarian tumor spheroids.

OVTwin is capable of modeling complex cellular interactions for systems containing up to 500,000 cells in under an hour, a feat previously hindered by computational bottlenecks. In validation studies, the framework accurately reproduced real-world tumor regression and resistance dynamics under paclitaxel-carboplatin treatment, confirming the synergistic efficacy of standard combination therapies. By facilitating rapid, large-scale modeling of intricate tumor-drug interactions, OVTwin demonstrates how digital twins can move from theoretical concepts into practical, high-throughput tools. Ultimately, such frameworks pave the way for exploring patient-specific chemotherapy responses, mitigating treatment resistance, and advancing genuinely individualized treatment strategies in ovarian cancer care.

Complementing high-throughput spheroid models, agent-based architecture provides deep resolution into single-cell behavior. The ALISON (digitAl twIn Simulator Ovarian caNcer) framework utilizes agent-based modeling to simulate individual cell-to-cell heterogeneity and metastatic dissemination within the peritoneal cavity. By tracking individual cell profiles alongside fluctuating levels of oxygen, glucose, and waste, ALISON allows researchers to capture the

evolving diversity of high-grade serous ovarian cancers over time. Furthermore, digital twins are advancing beyond conventional cytotoxic regimens to map the broader tumor microenvironment (TME). Using ordinary differential equation (ODE)-based models, recent investigations have successfully simulated TME signaling pathways under the influence of novel adjuvant agents like caffeic acid phenethyl ester (CAPE). These models demonstrate how targeted, microenvironmental modulations can work synergistically with standard paclitaxel regimens to curb spatial invasion.

By combining multi-scale computational approaches, from high-throughput GPU models and single-cell agent simulations to TME signaling networks, digital twins are moving from theoretical concepts into practical, high-throughput tools. Ultimately, these integrated frameworks would predict patient-specific chemotherapy responses, mitigate treatment resistance, and advance genuinely individualized treatment strategies in ovarian cancer care. These approaches provide complementary perspectives on tumor behavior, treatment response, resistance mechanisms, and individualized care.

Next-Generation Cancer Treatment Using Digital Twins in Rare Cancers

Background

Rare cancers represent a diverse and clinically challenging group of malignancies characterized by their low incidence, substantial biological heterogeneity, and frequent limitations in available clinical evidence. Although each rare cancer affects relatively few individuals, collectively these malignancies account for a meaningful proportion of the global cancer burden. Rare cancers include uncommon solid tumors, rare hematological malignancies, pediatric and adolescent cancers, sarcomas, neuroendocrine tumors, unusual central nervous system tumors, rare gastrointestinal malignancies, and cancers occurring in anatomically uncommon sites. Their rarity frequently creates difficulties in diagnosis, treatment selection, clinical trial recruitment, and development of evidence-based therapeutic strategies. Patients may experience delayed diagnosis, limited access to specialists, and treatment pathways based on small observational studies or extrapolation from more common cancers. These limitations create an important opportunity for advanced computational approaches capable of integrating heterogeneous patient information and supporting individualized clinical decisions.

Digital twins represent an emerging approach with considerable potential for addressing some of these challenges. A digital twin is a dynamic computational representation of an individual patient that integrates clinical, biological,

imaging, treatment, and longitudinal outcome information. Unlike conventional predictive models that often generate a single risk estimate, a digital twin can be continuously updated as new information becomes available. It can therefore represent disease evolution, simulate potential interventions, estimate possible outcomes, and support adaptive treatment strategies. In rare cancers, where direct clinical evidence may be limited, this capacity could be particularly valuable. A patient-specific digital twin may integrate information from comparable patients, molecular profiles, radiological characteristics, pathological findings, treatment responses, and real-world evidence to construct a more comprehensive representation of disease behavior.

The development of digital twins for rare cancers depends on combining artificial intelligence, machine learning, computational modeling, multi-omics analysis, medical imaging, digital pathology, and clinical databases. These technologies can transform fragmented clinical information into a structured and continuously evolving model of the patient's disease. The digital twin can potentially simulate different therapeutic options, compare expected benefits and risks, identify early indicators of treatment resistance, and assist clinicians in selecting personalized treatment pathways. It may also support multidisciplinary decision-making by providing a common computational framework for integrating information generated by oncologists, pathologists, radiologists, surgeons, geneticists, and other specialists.

An important advantage of this approach is its potential to overcome some consequences of limited sample sizes. Rather than treating rarity as an absolute barrier to personalization, digital twin systems can use advanced statistical and computational approaches to integrate information across institutions and populations while retaining patient-specific characteristics. Federated learning and privacy-preserving data analysis may further facilitate collaboration between specialized centers without requiring unrestricted transfer of individual-level data. Consequently, digital twins could become an important component of next-generation precision oncology for rare cancers. However, their implementation requires rigorous validation, transparent modeling, appropriate governance, and careful recognition of uncertainty. The objective should not be to replace clinical expertise, but to provide clinicians with a dynamic and evidence-informed computational representation that improves understanding of complex rare malignancies and supports more precise treatment decisions.

Digital Twin Architecture For Rare Cancer Care

A digital twin for rare cancer care requires a

multidimensional architecture capable of representing the complexity of both the patient and the disease. The foundation of such a system is a comprehensive patient data layer that incorporates demographic characteristics, medical history, symptoms, laboratory measurements, pathology reports, imaging findings, molecular information, previous treatments, treatment responses, adverse events, comorbidities, and longitudinal outcomes. Because rare cancers often have highly variable clinical presentations, the digital twin should not rely on a limited set of predefined variables. Instead, it should be capable of incorporating new data types as diagnostic technologies and clinical practices evolve.

The second component is a disease representation layer. This component describes the biological and clinical characteristics of the patient's malignancy, including tumor location, histological subtype, grade, stage, molecular alterations, immune characteristics, metastatic pattern, and growth behavior. For some rare cancers, molecular characteristics may provide more clinically meaningful information than anatomical classification alone. Therefore, the digital twin should be capable of integrating genomic, transcriptomic, proteomic, metabolomic, and epigenomic information when available. Such integration can help identify molecular similarities between patients who have apparently different clinical presentations.

An artificial intelligence layer can then transform these data into predictive and simulation models. Machine learning algorithms can identify relationships between patient characteristics and outcomes, while deep learning can process complex imaging and pathology data. Survival models can estimate progression and mortality risks, whereas causal and mechanistic models can investigate how different interventions may influence disease trajectories. Reinforcement learning approaches may eventually help identify treatment strategies that adapt to changing disease states. Importantly, these systems should communicate uncertainty rather than presenting predictions as definitive outcomes.

A simulation layer forms the central feature of the digital twin. This component allows clinicians to explore hypothetical scenarios, such as surgery versus systemic therapy, different radiation strategies, alternative drug combinations, treatment intensification, or observation. The system could estimate potential tumor response, progression risk, toxicity, and functional outcomes under each scenario. New clinical information could then be incorporated into the model to update these predictions.

Finally, a clinical interface should translate complex computational outputs into understandable information for healthcare professionals and patients. Visualization tools may display tumor

trajectories, predicted treatment responses, confidence intervals, and alternative therapeutic pathways. For rare cancers, this architecture can also incorporate external evidence from international registries, specialized cancer centers, clinical trials, and curated literature. The resulting system would function as a dynamic knowledge environment rather than a static prediction tool, continuously learning from new evidence while maintaining patient-specific representation.

Digital Twins In Rare Solid Tumors

Rare solid tumors include a wide spectrum of malignancies such as sarcomas, rare gastrointestinal cancers, uncommon thoracic tumors, unusual endocrine malignancies, and tumors affecting anatomically uncommon sites. Their biological diversity makes conventional treatment algorithms difficult to apply uniformly. Digital twins may provide a framework for representing this heterogeneity while supporting individualized treatment simulation.

Sarcomas provide an important example because they contain numerous histological and molecular subtypes, each with distinct clinical behavior and treatment sensitivity. A digital twin could integrate magnetic resonance imaging, computed tomography, histopathological findings, molecular characteristics, surgical information, and treatment history to estimate

local recurrence and metastatic risk. For a patient undergoing surgery, the system could potentially simulate different surgical margins and estimate their effects on local control and functional outcomes. Similarly, radiation treatment strategies could be evaluated in relation to tumor geometry and surrounding anatomical structures.

Rare gastrointestinal tumors may also benefit from digital twin technology. Tumors such as gastrointestinal stromal tumors, neuroendocrine neoplasms, and uncommon biliary or pancreatic malignancies frequently demonstrate substantial molecular diversity. Digital twins could combine imaging-derived tumor characteristics with genomic alterations and longitudinal treatment response to identify patients likely to benefit from targeted therapies. Serial imaging could be used to detect subtle changes in tumor morphology before conventional measures of progression become apparent.

Rare thoracic tumors present another opportunity. Digital twins could integrate radiological characteristics, pulmonary function, molecular findings, and treatment history to evaluate surgical candidacy, radiation exposure, systemic treatment options, and expected functional consequences. In anatomically complex tumors, three-dimensional representations could support treatment planning and help clinicians visualize relationships between the tumor and

surrounding structures.

The value of digital twins may be particularly high when evidence from randomized clinical trials is limited. A digital twin could identify biologically or clinically similar patients across international datasets and incorporate their treatment outcomes into individualized predictions. However, similarity should not be interpreted as equivalence. Rare cancers may contain subgroups that appear clinically similar but respond differently because of unmeasured biological characteristics. Therefore, digital twin systems should distinguish observed evidence from model-derived inference.

The integration of longitudinal data is another important advantage. Rare cancers can change rapidly, and treatment responses may differ substantially between patients. A digital twin can be updated after each imaging examination, laboratory assessment, biopsy, or treatment cycle. This creates a dynamic representation of disease progression rather than relying solely on information obtained at diagnosis. Such continuous updating may enable earlier identification of treatment failure and facilitate timely changes in therapy. Ultimately, digital twins could help transform rare solid tumor management from a predominantly protocol-based approach into a dynamic and individualized process.

Digital Twins In Rare Hemato-

logical And Pediatric Cancers

Rare hematological and pediatric cancers present distinctive challenges that make individualized computational modeling particularly relevant. Rare leukemias, lymphomas, myelodysplastic disorders, and other uncommon hematological malignancies can differ substantially in molecular characteristics, treatment response, relapse patterns, and toxicity profiles. Pediatric cancers introduce additional complexity because disease behavior and treatment effects are strongly influenced by developmental stage, body size, organ maturation, and long-term survivorship considerations.

For rare hematological cancers, a digital twin can integrate blood counts, bone marrow findings, flow cytometry, cytogenetic abnormalities, molecular profiles, imaging, treatment history, measurable residual disease, and clinical symptoms. This information can be used to estimate disease burden and predict response to chemotherapy, targeted therapy, immunotherapy, cellular therapies, or transplantation. Serial measurements of measurable residual disease are particularly valuable because they provide dynamic information about treatment effectiveness. A digital twin could update relapse risk after each assessment and potentially identify patients requiring treatment intensification or alternative strategies.

Rare lymphomas could similarly benefit from

integrating positron emission tomography, computed tomography, pathology, molecular characteristics, and clinical outcomes. Imaging-based changes could be evaluated together with molecular information to distinguish residual disease from treatment-related changes. Such integration may improve individualized assessment of treatment response and assist decisions regarding consolidation or salvage therapy.

Pediatric rare cancers require an even broader representation. A pediatric digital twin should account not only for tumor characteristics but also for growth, development, organ function, neurocognitive outcomes, fertility, endocrine effects, and long-term quality of life. Treatment simulation could therefore extend beyond short-term tumor control. For example, two therapeutic strategies might have similar predicted survival but substantially different risks of long-term toxicity. A digital twin could help clinicians and families evaluate these competing outcomes.

The limited number of pediatric patients with specific rare malignancies makes data sharing particularly important. International collaborative registries and federated learning systems could allow institutions to contribute information without transferring sensitive individual-level data. AI models could learn from geographically distributed datasets while preserving local data governance requirements.

However, pediatric applications require special ethical safeguards. Predictions should be carefully validated across age groups, developmental stages, and populations. Parents and, when appropriate, children should receive understandable explanations of how computational predictions are generated and how they influence treatment decisions. Digital twins should support shared decision-making rather than create an impression that treatment choices are determined automatically. With appropriate safeguards, these systems could contribute to a more individualized approach to rare hematological and pediatric oncology while reducing dependence on generalized treatment assumptions.

Artificial Intelligence, Imaging, And Multi-Omics Integration

Artificial intelligence provides the computational foundation required to transform complex clinical information into an operational digital twin. Rare cancer datasets often contain relatively few patients but exceptionally rich information. These data may include high-resolution imaging, whole-slide pathology images, genomic sequencing, laboratory measurements, clinical notes, treatment histories, and longitudinal outcomes. AI methods can identify patterns across these heterogeneous sources that may not be apparent through conventional statistical analysis.

Medical imaging is particularly important because it provides repeated, noninvasive measurements of tumor characteristics. Deep learning can identify tumor boundaries, quantify volume, characterize texture, and extract imaging features associated with treatment response. Radiomics can transform images into quantitative variables describing tumor heterogeneity, shape, intensity, and spatial characteristics. When integrated into a digital twin, these measurements can be monitored over time and linked to biological and clinical changes.

Computational pathology provides another major source of information. Digital pathology systems can analyze tumor architecture, cellular morphology, stromal characteristics, immune-cell distribution, and other microscopic features. These features may provide information about prognosis or treatment sensitivity. Combining pathology with imaging may improve characterization of tumor heterogeneity and potentially identify clinically meaningful subregions within a tumor.

Multi-omics integration can further increase the biological depth of the digital twin. Genomic alterations may identify therapeutic targets, while transcriptomic profiles can provide information about gene activity. Proteomic and metabolomic data may provide additional information about cellular processes and treatment response. Integrating these layers requires sophisticated com-

putational methods capable of handling high-dimensional data while preventing overfitting, particularly in rare cancers with limited sample sizes.

Natural language processing can also extract information from clinical notes, pathology reports, radiology reports, and published literature. This capability may be especially useful for rare cancers because clinically important information is frequently distributed across specialized documents rather than standardized databases. AI systems can organize this information and connect individual patient characteristics with relevant external evidence.

Multi-modal AI models may eventually combine imaging, pathology, molecular data, clinical information, and treatment history within a single digital twin. However, technical sophistication does not guarantee clinical validity. Models trained on small or highly specialized datasets may perform poorly in external populations. Therefore, calibration, external validation, uncertainty estimation, explainability, and prospective evaluation are essential. The objective should be to develop AI systems that are not merely accurate in retrospective datasets but clinically reliable across institutions, technologies, and patient populations.

Adaptive Treatment And Personalized Clinical Decision-Making

One of the most important potential applications of digital twins in rare cancers is adaptive treatment. Conventional oncology often follows predefined treatment pathways based on disease stage and histological classification. Although these approaches provide consistency, they may not fully account for individual differences in tumor biology, treatment response, toxicity, and patient priorities. Digital twins could allow treatment plans to evolve according to continuously updated evidence.

At diagnosis, the digital twin could generate a baseline representation of disease status and estimate expected outcomes under available treatment options. After treatment begins, new information could be incorporated into the model. Changes in tumor size, imaging characteristics, biomarkers, molecular profiles, symptoms, laboratory measurements, and adverse effects could modify predicted outcomes. If the expected benefit of the current treatment decreases, the digital twin could identify alternative strategies for clinical consideration.

Treatment simulation could also support sequencing decisions. For rare cancers, the optimal order of therapies may be uncertain because direct comparative trials are uncommon. A digital twin could compare potential sequences using available patient-level and external evidence. It might evaluate whether early introduction of targeted therapy, immunotherapy, radiation,

surgery, or combination treatment could improve the predicted outcome.

Surgical planning is another potential application. Three-dimensional digital representations could provide detailed information about tumor anatomy and relationships with critical structures. Simulations could compare alternative surgical approaches and estimate potential effects on margins, complications, organ function, and postoperative recovery. This could be especially useful for rare tumors occurring in anatomically complex regions.

Radiation oncology may similarly benefit from digital twin technology. A patient-specific model could integrate tumor geometry, previous radiation exposure, organ-at-risk characteristics, and biological information to compare treatment plans. Adaptive radiation therapy could then adjust treatment as anatomy and tumor characteristics change.

Importantly, personalized decision-making should incorporate patient preferences. Survival is not always the only meaningful outcome. Patients may prioritize functional preservation, quality of life, fertility, cognitive function, treatment duration, or avoidance of severe toxicity. Digital twins could incorporate these preferences into multi-objective treatment simulations, helping clinicians explain trade-offs among alternative strategies.

The ultimate role of the digital twin should

therefore be decision support rather than autonomous treatment selection. Clinicians remain responsible for interpreting predictions within the broader clinical context. A computational model can estimate probabilities and simulate scenarios, but it cannot fully capture patient values, emerging evidence, or unusual clinical circumstances. Used appropriately, however, digital twins could make individualized treatment planning more systematic, transparent, and responsive.

Challenges, Ethical Considerations, And Clinical Validation

Despite their potential, digital twins for rare cancers face substantial scientific, technical, ethical, and regulatory challenges. The most fundamental problem is data scarcity. Rare cancers naturally produce smaller datasets, and many available datasets may be fragmented across institutions. Small sample sizes increase the risk of overfitting and unstable predictions. The problem becomes more severe when models incorporate large numbers of molecular or imaging variables.

Data heterogeneity represents another major challenge. Imaging protocols, sequencing platforms, pathology practices, clinical terminology, treatment strategies, and outcome definitions may differ between institutions. A model trained in one specialized center may therefore perform

poorly elsewhere. Standardized data structures and robust external validation are essential for developing reliable systems.

Bias is also a significant concern. Rare cancer registries may disproportionately represent patients treated at specialized academic centers. Underrepresentation of certain geographic, socioeconomic, ethnic, or demographic groups can result in models that perform unevenly across populations. Continuous monitoring of model performance is therefore necessary.

Privacy and cybersecurity are particularly important because digital twins integrate highly sensitive information. Genomic data, longitudinal clinical records, and detailed imaging may create significant privacy risks. Secure infrastructures, encryption, access controls, federated learning, and appropriate governance frameworks will be necessary to protect patients.

Interpretability is another important issue. Clinicians need to understand why a digital twin produces a particular prediction. Highly complex models that provide only an output without an understandable rationale may be difficult to trust and integrate into clinical practice. Explainable AI, uncertainty estimates, visualization, and transparent reporting can improve clinical usability.

Clinical validation must progress beyond retrospective accuracy. Digital twins should undergo

analytical validation, external validation, prospective observational evaluation, and ultimately clinical impact assessment. Randomized studies may be needed to determine whether digital twin-guided decisions actually improve patient outcomes. Relevant endpoints should include survival, treatment response, toxicity, quality of life, healthcare utilization, and decision-making efficiency.

Regulatory frameworks must also evolve as digital twins become more sophisticated. Systems that continuously learn from new data may behave differently over time, creating challenges for conventional software approval pathways. Clear processes for monitoring, updating, auditing, and withdrawing unsafe models will be essential. Ethical governance should ensure that computational recommendations remain subordinate to clinical judgment and patient autonomy. These safeguards are particularly important in rare cancers because the consequences of incorrect predictions may be substantial when alternative evidence is limited.

Future Perspectives And Conclusion

The future of rare cancer treatment is likely to involve increasing integration of clinical medicine with artificial intelligence, advanced analytics, multi-omics, imaging, and continuously updated computational models. Digital twins

provide a conceptual framework capable of bringing these technologies together into a patient-centered system. Rather than analyzing individual data sources separately, the digital twin can represent the patient and the malignancy as a dynamic system that changes over time.

Future systems may become increasingly comprehensive. Wearable devices, remote monitoring technologies, digital biomarkers, patient-reported outcomes, and home-based laboratory measurements could provide continuous information about symptoms, functional status, treatment toxicity, and recovery. These data could be incorporated into the digital twin to identify clinically meaningful changes between routine hospital visits. For patients with rare cancers who may need to travel long distances to specialized centers, remote monitoring could improve continuity of care.

Federated learning may also become increasingly important. Specialized rare cancer centers could collaboratively develop AI models without transferring all patient-level data to a central repository. This approach could increase effective sample sizes while maintaining stronger privacy protections. International collaboration may be particularly valuable for ultra-rare malignancies in which no single institution can accumulate sufficient cases for robust modeling.

Digital twins could also contribute to clinical research. Simulated treatment scenarios may help

identify promising therapeutic strategies and generate hypotheses for clinical trials. Patient similarity networks could facilitate identification of eligible participants for rare cancer studies. In the longer term, digital twin technology may support more efficient trial design by improving patient stratification and identifying clinically meaningful subgroups.

The integration of mechanistic biological models with data-driven AI could further improve reliability. Instead of relying exclusively on statistical associations, future digital twins may combine biological knowledge about tumor growth, immune interactions, treatment mechanisms, and drug resistance with real-world patient data. Such hybrid models could improve generalizability and provide more interpretable representations of disease evolution.

Nevertheless, digital twins should not be viewed as a technological solution to every limitation in rare cancer care. Their value will depend on the quality of the underlying evidence, the reliability of data, the transparency of algorithms, and the ability of healthcare systems to integrate computational tools into real clinical workflows. Technology should support, rather than replace, multidisciplinary expertise and patient-centered decision-making.

Rare cancers have historically faced an evidence disadvantage because their low incidence makes conventional clinical research difficult. Digital

twins offer an opportunity to reduce this disadvantage by integrating distributed evidence, modeling individual disease trajectories, and continuously adapting predictions as new information emerges. If developed through rigorous validation, responsible data governance, and international collaboration, digital twins could become an important component of next-generation precision oncology. Their greatest contribution may be the ability to transform limited and fragmented information into a dynamic representation of each patient's disease, enabling clinicians to explore treatment possibilities more systematically and make increasingly individualized decisions for patients with rare cancers.

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