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From virtual to reality: innovative practices of digital twins in tumor therapy

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Abstract

Background As global cancer incidence and mortality rise, digital twin technology in precision medicine offers new opportunities for cancer treatment.

Objective This study aims to systematically analyze the current applications, research trends, and challenges of digital twin technology in tumor therapy, while exploring future directions.

Methods Relevant literature up to 2024 was retrieved from PubMed, Web of Science, and other databases. Data visualization was performed using R and VOSviewer software. The analysis includes the research initiation and trends, funding models, global research distribution, sample size analysis, and data processing and artificial intelligence applications. Furthermore, the study investigates the specific applications and effectiveness of digital twin technology in tumor diagnosis, treatment decision-making, prognosis prediction, and personalized management.

Results Since 2020, research on digital twin technology in oncology has surged, with significant contributions from the United States, Germany, Switzerland, and China. Funding primarily comes from government agencies, particularly the National Institutes of Health in the U.S. Sample size analysis reveals that large-sample studies have greater clinical reliability, while small-sample studies emphasize technology validation. In data processing and artificial intelligence applications, the integration of medical imaging, multi-omics data, and AI algorithms is key. By combining multimodal data integration with dynamic modeling, the accuracy of digital twin models has been significantly improved. However, the integration of different data types still faces challenges related to tool interoperability and limited standardization. Specific applications of digital twin technology have shown significant advantages in diagnosis, treatment decision-making, prognosis prediction, and surgical planning.

Conclusion Digital twin technology holds substantial promise in tumor therapy by optimizing personalized treatment plans through integrated multimodal data and dynamic modeling. However, the study is limited by factors such as language restrictions, potential selection bias, and the relatively small number of published studies in this emerging field, which may affect the comprehensiveness and generalizability of our findings. Moreover, issues related to data heterogeneity, technical integration, and data privacy and ethics continue to impede its broader clinical application. Future research should promote international collaboration, establish unified interdisciplinary standards, and strengthen ethical regulations to accelerate the clinical translation of digital twin technology in cancer treatment.

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Keywords Tumor, Precision oncology, Digital twin, Digital twin model, Precision medicine, Virtual patients, Multidisciplinary collaboration, Bibliometric analysis

Introduction

Cancer is the second leading cause of death worldwide, accounting for approximately one-sixth of all deaths [1]. This statistic is primarily due to the complexity of cancer and its high heterogeneity as a multi-cellular ecosystem [2, 3]. Such heterogeneity is evident not only between different cancer types but also in how a single cancer type affects different patients [4]. Understanding the interactions between various cell types within tumors and their roles in tumor evolution is key to effective treatment [5, 6]. Despite recent advancements in cancer treatment, existing therapies still fail to deliver satisfactory outcomes for different patients, particularly within the context of precision oncology and molecular phenotyping (such as genomics and proteomics), underscoring the need for continued research and development [7]. Additionally, current treatment strategies often follow a "one-size-fits-all" approach, lacking truly personalized therapeutic options [8].

Against this backdrop, the emerging concept of digital twin (DT) technology has garnered widespread attention in oncology [9]. Initially applied in aerospace and manufacturing, a digital twin refers to a mathematical model constructed using real-time data that provides a virtual representation of a specific physical object, enabling the prediction of its behavior under various external conditions and optimizing future decision-making [10–14]. When applied to healthcare, the comprehensive report *Foundational Research Gaps and Future Directions for Digital Twins* by the National Academies defines digital twins as 'computational models created for the human body or its parts, which establish a bidirectional connection with the patient's system and are calibrated through periodic data collection to dynamically predict the patient's health status' [15]. The application of this technology in cancer treatment is particularly notable [16]. Its advantages lie not only in integrating genetic information, clinical history, and imaging data to create highly personalized cancer digital twin models but also in its ability to precisely simulate tumor molecular dynamics and treatment responses through multiscale models and advanced machine learning algorithms [17]. Based on this platform, medical experts can rehearse and optimize treatment plans in a virtual environment, track patient progress in real time, and significantly enhance treatment outcomes and quality of life [18].

Although digital twin applications in oncology are still in their infancy, the integration of digital twin technology into tumor dynamics and personalized care is gaining attention as experimental technologies and advancements in mathematics and computer science continue to evolve [19]. For example, the Gilbertson team [20] is developing the world's first computer model capable of spatially and temporally sensing the development of both normal and malignant tumors, aiming to identify efficient and low-toxicity treatment options for pediatric cancers. Wickramasinghe et al. [21], based on systems and mathematical modeling theories, proposed three digital twin models—gray-box, agent-based, and black-box—and explored the potential application of the black-box model in personalized care for uterine cancer. Additionally, a collaborative project initiated by the National Cancer Institute and the U.S. Department of Energy is focusing on the construction of patient-specific cancer digital twins, which provides a robust foundation for personalized cancer treatment [22].

Meanwhile, an increasing number of empirical studies have demonstrated the potential application value of digital twin technology in cancer treatment. For instance, the model developed by Wu et al. [23] integrates MRI data with biologically-based mathematical models, not only achieving precise prediction of neoadjuvant chemotherapy response in triple-negative breast cancer (TNBC) patients but also significantly outperforming traditional tumor volume measurement methods in predicting pathological complete response (PCR). Similarly, Kim et al. [24] developed a two-stage model that combines digital twins with machine learning, successfully capturing patient-specific, spatiotemporal dynamics of TNBC response to neoadjuvant systemic therapy (NAST), providing highly accurate predictions of NAST response. These successful cases not only highlight the immense potential of digital twins in precision oncology and clinical decision support systems but also lay a solid practical foundation for the future development of personalized medicine.

Given the immense potential of digital twins in cancer research, it is particularly important to comprehensively explore their scope of application. Therefore, this study aims to synthesize existing knowledge and analyze the extent of research on digital twins in the field of oncology. Through bibliometric analysis, we will examine trends in the total volume of publications,

the distribution of research funding, active research countries, and collaborative networks to provide an overview of the current state and future directions of digital twin research in oncology. Furthermore, within the framework of a scoping review, this paper will evaluate the specific applications of digital twin technology in cancer treatment and explore the challenges and future research opportunities by analyzing emerging real-world cases.

As an emerging personalized medical technology, digital twin technology shows great promise in oncology. To provide a thorough analysis of its application status, technical challenges, and future directions, this paper focuses on the following key questions:

1. What are the research trends, active countries, collaborative networks, and funding distributions for digital twins in the oncology field?
2. What are the characteristics of sample size distribution in current studies, and how does it relate to data sources and clinical applications? Is there a significant difference in sample sizes across different cancer types?
3. How does digital twin technology utilize multi-source data (such as imaging data and omics data) in tumor therapy? What is the role of AI algorithms in this process?
4. What are the main application scenarios and effectiveness of digital twin technology in oncology?
5. What are the key challenges faced by digital twin technology in oncology, and what are the future research directions?

Furthermore, to visually present the core logic and working mechanism of digital twins in oncology, a conceptual framework diagram of tumor digital twins (see Fig. 1) has been designed. This diagram systematically illustrates the process from multi-modal data collection to personalized treatment feedback optimization.

Methods

This study employs a combination of bibliometric analysis and a scoping review to comprehensively assess the research status of digital twin technology in tumor therapy. In the bibliometric section, the framework proposed by Cobo et al. [25] was followed. The scoping review was designed and conducted according to the PRISMA-ScR guidelines [26]. Specific research methods include literature retrieval, screening, and analysis, as well as data processing and visualization.

Data sources and search strategy

To ensure comprehensive retrieval and account for the interdisciplinary nature of tumor digital twins, we conducted a literature search across five major databases: PubMed, Web of Science, Scopus, Embase, and IEEE Xplore. Prior to the official search, all research team members participated in professional training based on the "Medical Literature Information Retrieval [27]" textbook. In collaboration with librarians, oncologists, and medical informaticians, we developed the search strategy. The search strategy was based on the definitions provided in the BEST [28] vocabulary, with core search terms including "digital twin" and "tumor," combined using Boolean operators (such as AND, OR). To ensure comprehensiveness, we also reviewed the reference lists and cited articles of relevant literature. Furthermore, to avoid bias due to data updates, the cutoff date for all search results was set to October 13, 2024. Literature management and duplicate removal were performed using EndNote software. For the detailed search strategy, please refer to Supplementary Material 1.

Inclusion and exclusion criteria

Inclusion criteria

- The literature must clearly research the application of digital twin technology in the tumor field (e.g., diagnosis, treatment, prognosis prediction), covering technical development or real-life cases.
- The included literature must focus on the technical framework, data integration methods, or algorithm optimization processes of digital twins, with at least one tumor-related experimental or clinical application.
- The literature must be peer-reviewed articles published in English.

Exclusion criteria

- Studies that cannot be accessed in full.
- Duplicate publications.
- Studies unrelated to tumors, such as those limited to engineering or industrial applications of digital twin technology.
- Literature that does not clearly provide research methods or data sources, particularly models or algorithms that cannot be reproduced.

Screening strategy

Prior to the formal inclusion or exclusion of studies, three reviewers (SS, WQ, and XL) randomly selected 30

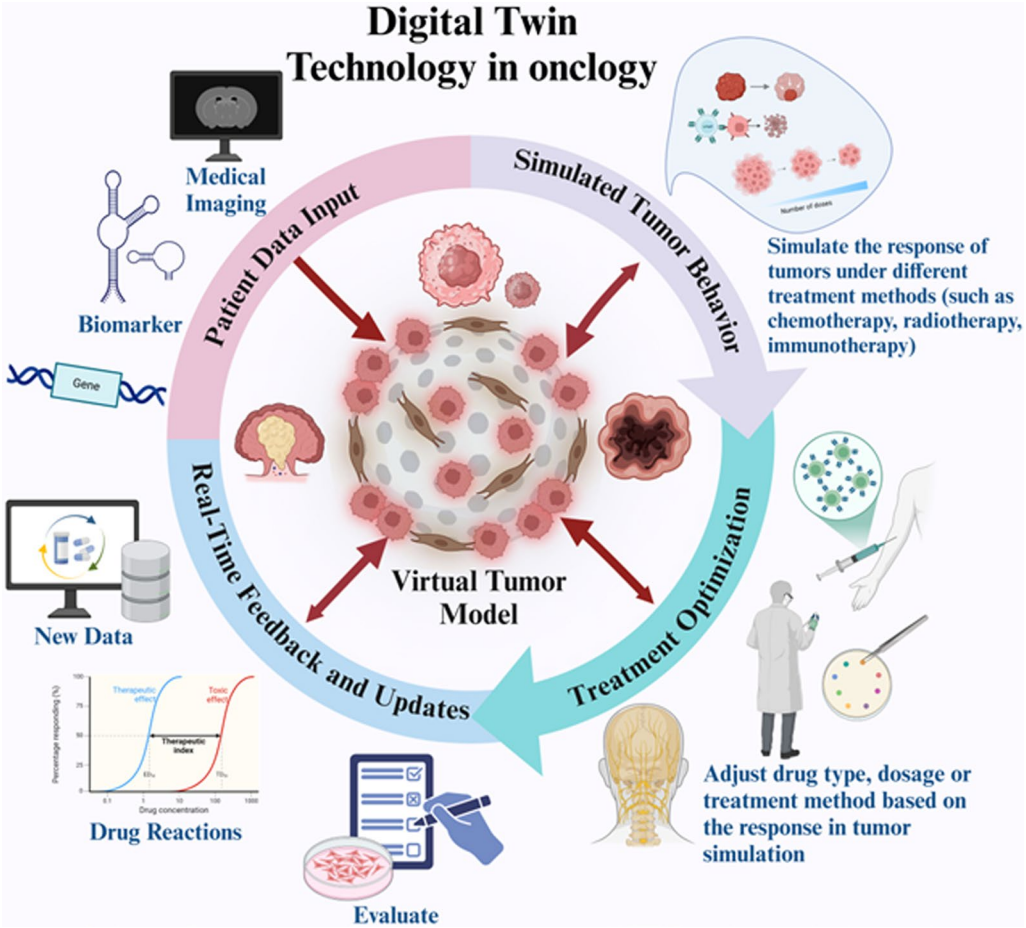

Fig. 1 Tumor Digital Twin. The entire system forms a dynamic closed-loop, ensuring that each stage of tumor treatment is updated and optimized based on real-time data. Each arrow represents the flow and feedback of information, helping clinicians continuously adjust treatment plans through the virtual model to provide more precise, personalized therapy. This closed-loop system enables clinicians to make the most appropriate adjustments during the treatment process based on the latest data, improving treatment efficacy and minimizing side effects

studies for preliminary screening to assess the reliability of the screening process. The final Cohen's kappa value was 0.89, indicating high consistency, and no adjustments were made to the inclusion/exclusion criteria or the reviewers. During the formal independent screening process, any discrepancies were ultimately resolved by SL, who intervened in the decision-making. The screening and verification process was completed on November 2, 2024, with 68 studies ultimately included. The detailed screening process is shown in Fig. 2, and the detailed information of the included literature can be found in Supplementary Material 2.

Data processing and analytical framework

To systematically analyze the research status and future prospects of digital twin technology in oncology, this study established the following analytical framework to ensure comprehensiveness and systematic coverage:

Bibliometric analysis

This section employs bibliometric methods, involving data cleaning and analysis, to examine the research trends and development of digital twin technology in the oncology field. As digital twin technology is still in the early stages of exploration in oncology, the number of relevant publications is limited. Therefore, the analysis focuses on the following aspects:

- *Research Initiation and Trends* The number of publications from 2020 to 2024 was analyzed, exploring the characteristics and early development trajectory of digital twin technology as it extends from general fields to oncology.
- *Geographical Distribution* By analyzing the geographical information of authors and institutions, the primary research centers and active countries

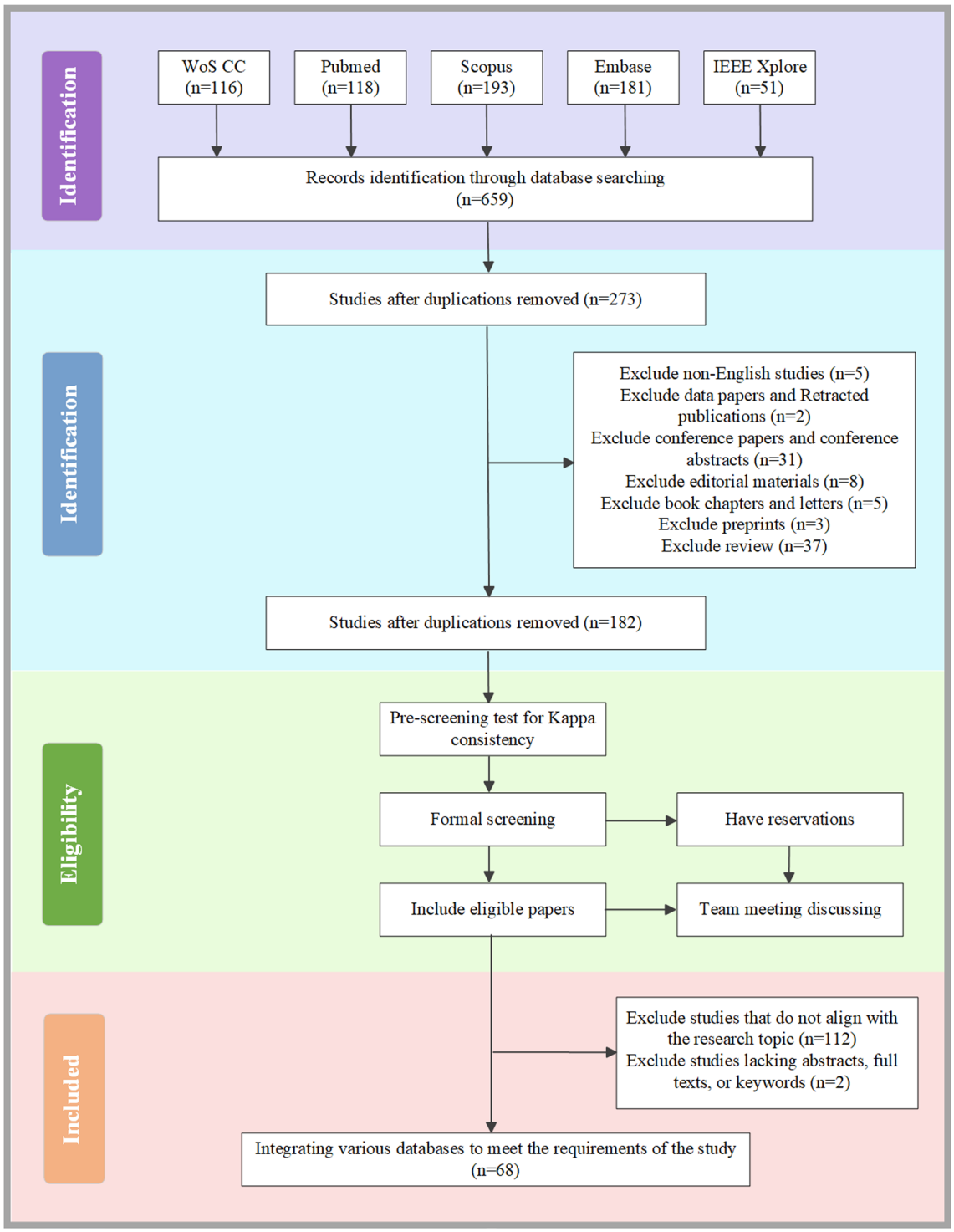

Fig. 2 Search and filter process diagram

in the early stages of digital twin technology in oncology were identified.

- *Funding distribution* The funding sources reported in the literature were analyzed, particularly the funding support from governments and multinational research organizations during the early stages of the technology.

Scoping review

This section synthesizes existing literature to discuss the application and development trends of digital twin technology in tumor therapy. Unlike the bibliometric analysis, this section does not involve complex data analysis or statistical methods but focuses on the following aspects:

- *Sample Size Analysis* Based on existing literature and the specific needs of oncology [29, 30], the studies were classified into small sample size (< 50 cases), medium sample size (50–500 cases), and large sample size (> 500 cases). Sample size directly affects the reliability and generalizability of digital twin research in oncology [31, 32].
- *Data Processing and AI Application Analysis* Digital twin applications rely heavily on multi-source, multi-modal data integration and AI algorithms [17]. This section systematically analyzes the use of medical imaging, omics data, and AI algorithms in digital twin technology.
- *Theme Classification Analysis* Based on the specific application scenarios of digital twins, the research was categorized into seven major areas: diagnosis, treatment decision-making, prognosis prediction, surgical planning, drug development and virtual trials, tumor microenvironment analysis, and personalized management.

Analysis tools

Given the large volume of data, human error in statistical calculations may occur, and manual analysis often faces challenges. Furthermore, traditional single-tool analysis often suffers from low granularity [33, 34]. To ensure completeness and high granularity, a multi-tool bibliometric analysis strategy was employed. Specifically, the analysis utilized tools such as VOSviewer [35] (Version 1.6.19), Gephi (Version 0.10.1), and Cortext (Gustave Eiffel University). In terms of layout and enhanced visualization, ScimagoGraphica [36] (Version 1.0.16) was used. Data processing, analysis, and visualization were performed using Origin2024, networkD3, and ggplot2 R software packages. Detailed analysis strategies and data cleaning methods are provided in Supplementary Material 1.

Results

Annual publication trends

The temporal distribution of the literature reflects the research trend of digital twin technology in the oncology field. The number of publications increased annually from one in 2020 to 27 in 2024, with a significant rise after 2022. This trend indicates that with the advancement of technology and policy support, digital twin technology in oncology is receiving increasing attention and investment. In terms of research topics, early studies were more focused on concepts and theoretical exploration. For example, Zhang et al. (2020) [37] proposed a framework for applying digital twins in lung cancer diagnosis, combining physical rendering technology and deep learning models to provide dynamic simulation and prediction tools for precision medicine. Béthencourt et al. [38] designed a digital twin-based connected device to monitor the occurrence and development of post-operative lymphedema in breast cancer patients, providing a technical reference for early detection and dynamic monitoring in oncology. Later studies, however, have been more focused on practical applications and clinical validation. For example, Wang et al. [39] integrated patient data and interview information to develop a digital twin for ovarian cancer patients and caregivers, optimizing the health information recommendation system and addressing the issue of insufficient clinical data in the early stages. Obergfell et al. [40] used a target trial simulation framework to compare planned and unplanned resections and their effects on recurrence and survival in sarcoma patients, providing a real-life example of digital twin application in surgical decision-making.

Country analysis

Figure 3A shows the geographical distribution of digital twin technology publications in oncology, with 27 countries publishing related research. The size of the circles in the figure represents the publication volume of each country, while the colors differentiate the publication quantities. The map illustrates that, despite being in its early stages, the field exhibits a certain degree of global distribution. The United States (n = 28) leads the field, indicating its dominant role in combining digital twin technology with oncology research. Germany (n = 14), Switzerland (n = 10), and China (n = 10) have also contributed significantly, reflecting the research strength and interest in this emerging field within these countries. From a regional perspective, North America, Europe, and Asia are the primary research hubs. While the United States remains dominant in international research, European countries such as the United Kingdom and Germany have formed a robust research cluster that supports the widespread development of this technology.

Figure 3B shows the network diagram of international cooperation, further revealing the distribution of collaborative relationships. The thickness of the lines represents the strength of collaboration. The diagram indicates that the U.S. is not only the leading country in publication volume but also a central hub in the global research

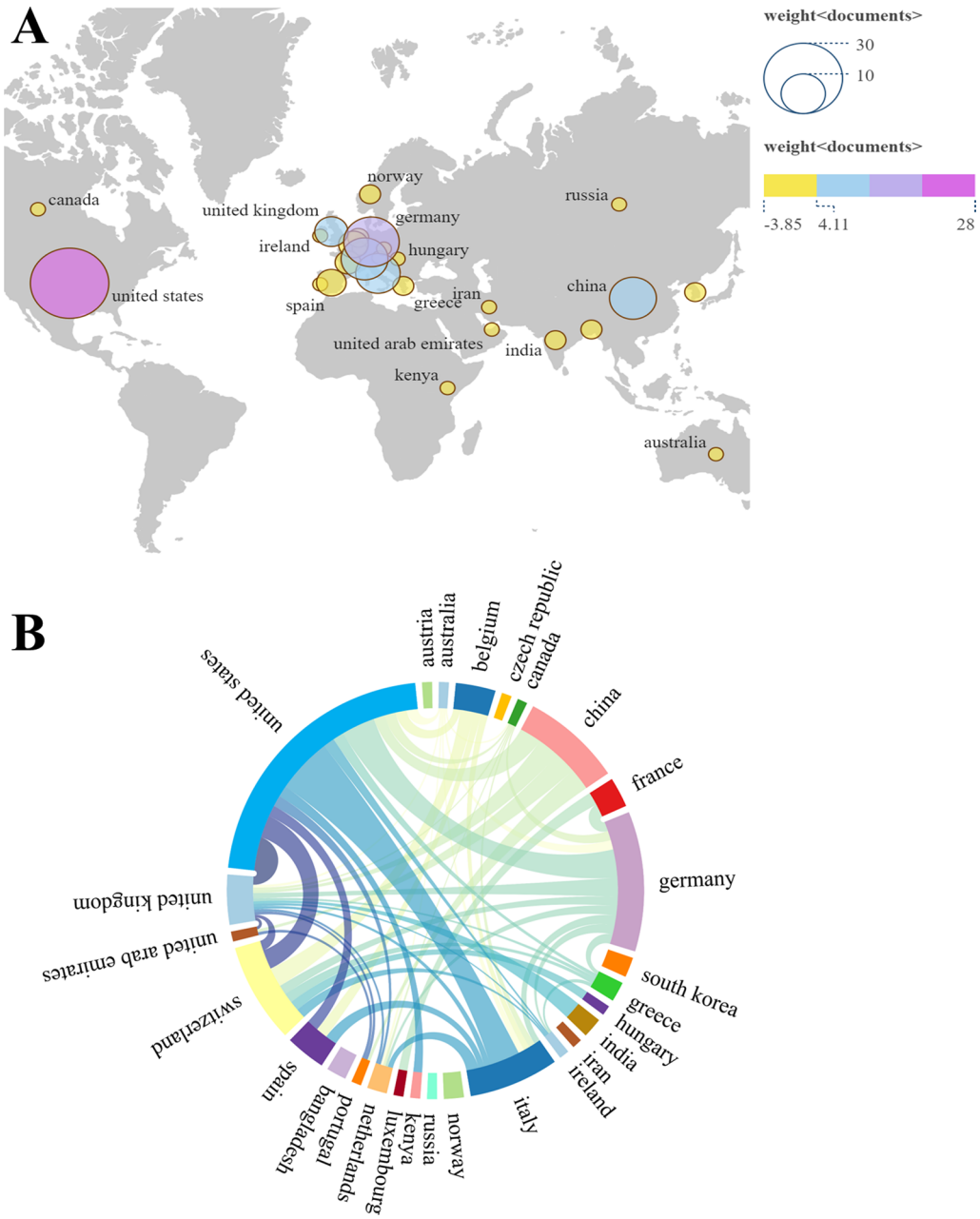

Fig. 3 Productivity and International Cooperation in Digital Twin Research in Oncology. **A** Geographical distribution map of publications by country. **B** International cooperation network diagram between countries

cooperation network, with strong ties to Italy, the United Kingdom, Germany, China, and several other countries. European nations (such as the UK, Germany, and Italy) also exhibit close collaboration, forming stable research networks. China's collaborations with major Western countries (such as the U.S. and Germany) are prominent, showing China's increasing integration into the global research landscape.

Funding analysis

A total of 49 studies (49/69, 71.01%) received funding, with a total of 104 instances of funding. On average, each funded project received 2.12 funding sources. These funds came from 66 different sources. As shown in Table 1, the major funding source was the U.S. National Institutes of Health (NIH), which provided 10 funding instances (10.4%), followed by the OPO Foundation, Margrit Weisheit Foundation, and Parrotia Foundation

Table 1 Top 8 funding sources in digital twin research in oncology

Rank	Funding source	Frequency	Country
1	National Institutes of Health	10	United States
2	OPO Foundation	4	Switzerland
2	Margrit Weisheit Foundation	4	Switzerland
2	Parrotia Foundation	4	Switzerland
5	MD Anderson Cancer Center	3	United States
5	Cancer Prevention and Research Institute of Texas	3	United States
5	National Science Foundation	3	United States
5	National Natural Science Foundation of China	3	China

from Switzerland, each contributing four funding instances. Among the top eight funding agencies, four are U.S. government departments, such as the NIH and National Science Foundation, indicating the prominent role of U.S. government funding in this field.

Additionally, we categorize all funding sources into government grants, funding from non-profit organizations and foundations, corporate funding, support from international organizations, funding from universities and research institutions, and individual contributions. As shown in Fig. 4A and 4B, government funding is the primary source of financial support, accounting for 52.88% of the total funding instances. University and research institution funding accounted for 18.27%, while corporate and private funding represented a smaller portion of the total funding.

Sample size analysis

To comprehensively evaluate the scope, representativeness, and application trends of digital twin technology in oncology, we conducted a sample size analysis of the included studies and visualized the correlation between sample sizes, data sources, and clinical application scenarios using a Sankey bubble chart (Fig. 5). Detailed sample size information for each study can be found in Supplementary Material 2.

Sample size distribution and classification

The included studies showed significant variation in sample sizes, ranging from individual cases to tens of thousands of patients. We classified studies into small sample sizes (< 50 cases, 20.59%), medium sample size (50–500 cases, 23.53%), and large sample sizes (> 500 cases, 27.94%). Additionally, about 27.94% of the literature did not clearly report sample sizes, often relying on non-traditional data sources such as virtual patient data or experimental data, or due to data privacy restrictions. This phenomenon reflects the need for improved reporting standards and transparency in current research.

- *Small Sample Size Studies (< 50 cases)* Small sample size studies are primarily used for technology development and preliminary validation, relying mainly on clinical trial data [38, 39, 41], medical imaging data [42–44], and animal model data [45, 46]. These studies typically focus on personalized diagnosis and

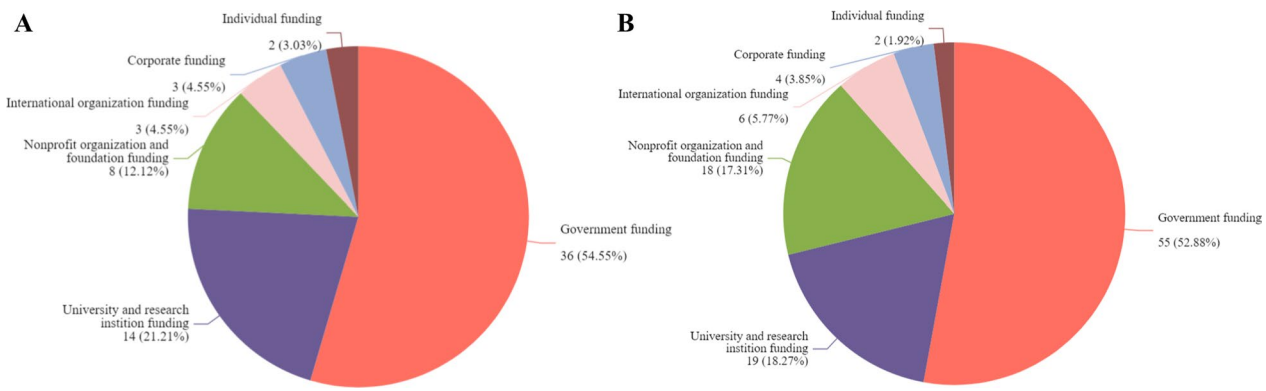

Fig. 4 Types and Numbers of Funding Sources in Digital Twin Research in Oncology. A Distribution of funding types. B Number of funding sources by type

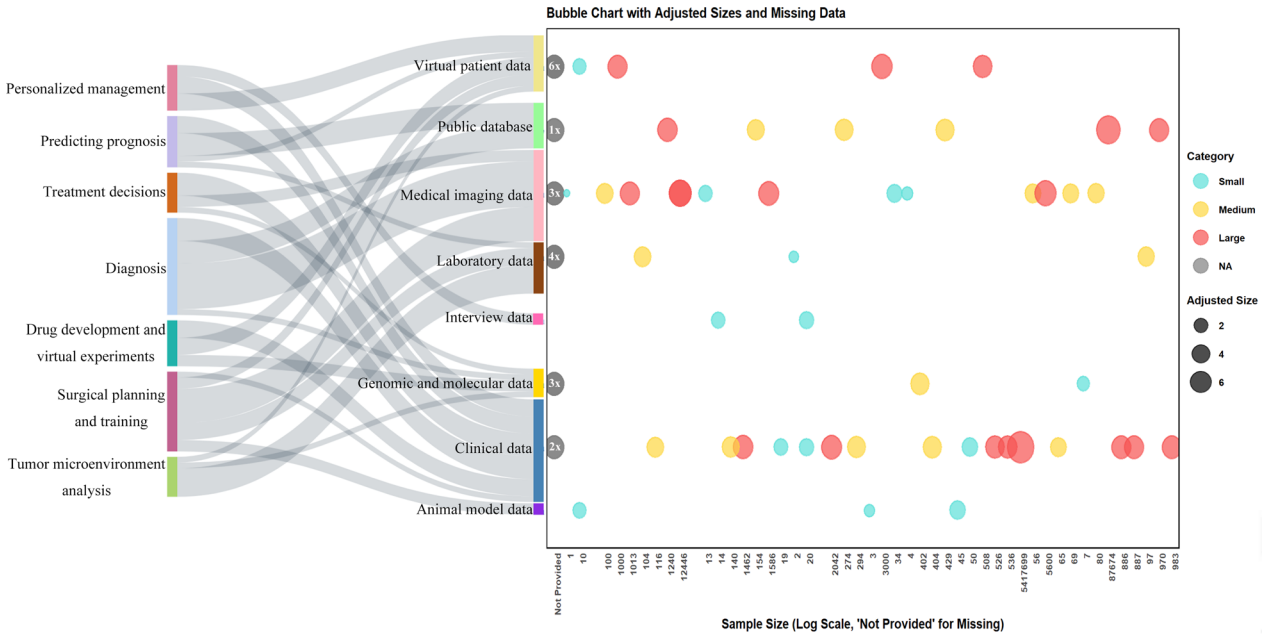

Fig. 5 Correlation diagram of sample size, data sources, and clinical application in digital twin research in oncology. The bubble color represents the sample size classification (small sample size, medium sample size, large sample size), and the bubble size reflects the specific scale of the sample. The Sankey diagram shows the flow of data sources (such as virtual patient data, medical imaging data, genomic and molecular data, etc.) and clinical applications (such as diagnosis, treatment decision-making, and personalized management), clearly illustrating the correlation between data types and application scenarios

treatment [38, 41, 47, 48] and technical precision testing [45, 46, 49, 50]. For example, a study involving 20 breast cancer patients developed a digital twin-assisted health device measurement method for lymphedema prevention [38].

- *Medium Sample Size Studies (50–500 cases)* Medium sample size studies often integrate multi-dimensional data, such as genomic, metabolomic, and medical imaging data [51–53], to support model validation and early clinical testing. As shown in Fig. 5, these studies are primarily focused on diagnosis (25%), prognosis prediction (25%), and treatment decision-making (approximately 25%), reflecting the wide applicability of medium sample sizes in relevant clinical fields. For instance, a study involving 116 breast cancer patients integrated multi-omics data to construct a digital twin model, which was used to optimize personalized treatment strategies [54].
- *Large Sample Size Studies (> 500 cases)* Large sample size studies often rely on public databases or comprehensive tumor datasets, covering broad application scenarios, especially in diagnosis [55–59] and personalized management [41, 60, 61]. The primary data sources are medical imaging data (50%) and clinical data (30%).For example, a study involving 887 lung cancer patients utilized generative adversarial networks (GANs) to generate synthetic data, enabling clinical applications and data sharing while preserving patient privacy [55].

Data sources and application scenarios

The Sankey bubble chart (Fig. 5) illustrates the flow relationship between data sources and clinical application scenarios, revealing the patterns of data usage in tumor research. Among the data types, medical imaging and clinical data are the most common sources, primarily directed towards diagnosis and treatment decision-making. Virtual patient data and laboratory data are more commonly used for technology validation and personalized management, reflecting the significant role of non-traditional data sources in early-stage technology development. The major application scenarios of digital twin technology include diagnosis, treatment decision-making, and prognosis prediction, where diagnosis heavily relies on large sample sizes, while personalized management and surgical planning tend to utilize small and medium sample size studies. Notably, only eight studies utilized public datasets, suggesting that despite the increasing application of digital twin technology in oncology, the use of publicly available datasets remains limited, likely due to concerns over data privacy and quality.

Sample size distribution by cancer type

The studies included in this research cover common cancer types such as breast cancer [23, 38, 58, 62–64], head and neck cancer [65–68], brain tumors [59, 69–71], lung cancer [37, 55, 72, 73], as well as specific subtypes and experimental cell-level data, such as high-grade gliomas [74] and triple-negative breast cancer [75]. Among these, breast cancer research represents the largest proportion, with sample size distributions ranging from small case numbers (e.g., 20 cases [38]) to large-scale cohorts (e.g., 80,000 cases [76]), indicating a strong clinical demand for digital twin applications in this cancer type. In contrast, brain tumors and other specific cancer subtypes are predominantly studied with smaller sample sizes, focusing on precision medicine or exploring underlying mechanisms, such as the study of high-grade gliomas with about 100 cases [74].

Data processing and integration in tumor treatment

Digital twin technology in tumor treatment relies on the integration and processing of multi-source, multi-modal data [17]. These data provide essential support for constructing precise patient models.

Medical imaging data

Among the literature included, imaging data accounted for 36.76% (25 studies). MRI and CT imaging were the most commonly used, with 17 studies applying them for tumor segmentation, 3D modeling, and treatment optimization. For instance, Tai et al. [73] used radiological images for tumor segmentation and treatment optimization, while Sainz-DeMena et al. [4] reconstructed a 3D mesh model of neuroblastoma based on CT images, aiding personalized treatment and surgical planning. Additionally, 15 studies involved dynamic imaging data, covering dynamic contrast-enhanced MRI (DCE-MRI), time-series CT, PET, and SPECT imaging. DCE-MRI was the most frequently used dynamic data source (n = 4, 26.67%), employed to monitor tumor size changes and therapeutic response modeling [23, 74, 75, 77].

Multi-omics data integration

The integration of multi-omics data (including genomics, proteomics, metabolomics, etc.) has provided strong data support for digital twin models, enhancing their ability to adapt to individual differences [78]. Among the included studies, over 15% focused on the application of multi-omics data, aiming to enhance the model's ability to analyze the tumor microenvironment, predict treatment responses, and optimize decision-making. Specifically, the applications are as follows:

- *Genomic Data* Genomic data accounted for more than 14.29% of all relevant studies, primarily used to identify tumor-driving gene mutations, support personalized treatment decisions, and precision-targeted strategies, as well as provide a basis for personalized vaccine design [51, 79]. By identifying cancer-driving genes, digital twin models can predict the response of different genotypes to specific treatments.
- *Proteomics and Metabolomics Data* Seven studies explicitly mentioned the application of proteomics and metabolomics data. Proteomics data are mainly used to analyze intracellular signaling pathways and protein interactions in tumor cells, while metabolomics data reveal the phenomenon of metabolic reprogramming in tumor cells. Both play key roles in tumor microenvironment analysis [80] and treatment response evaluation [77].
- *Single-Cell Omics Data* Single-cell omics data were applied in approximately 5.71% of studies, primarily to uncover tumor cellular heterogeneity and the dynamic changes in the immune microenvironment. Single-cell analysis can capture cellular differences within the tumor and their response to treatment, particularly with regard to temporal changes in immune therapy. Through single-cell-level data, researchers can obtain more precise tumor dynamic information, which aids in advancing personalized and refined immune therapy [81].

Although the integration of multi-omics data and dynamic modeling is on the rise, only six studies have achieved comprehensive integration of multiple omics data types [38, 51, 62, 77, 82, 83], with a primary focus on the combination of genomics and proteomics data. The integration of metabolomics and single-cell omics data remains relatively low, indicating that the integration of these data faces certain technical challenges.

Additional data sources

In addition to imaging data, various other data types have been progressively integrated into digital twin models. Specifically, physiological data were widely applied in 16 studies, primarily used to dynamically adjust personalized treatment strategies [47, 61, 84]. Pathological slide data were mentioned in eight studies, mainly for enhancing the precision of diagnosis and treatment decisions by combining genomic information [51, 84]. Three studies involved animal model data, providing experimental support for tumor surgical planning, optimizing surgical approaches, and predicting treatment outcomes [45, 46, 50]. Additionally, unstructured data were mentioned in

two studies, further enriching the input for digital twin models [39, 47].

Role of artificial intelligence in digital twin technology

Artificial intelligence (AI) plays a central role in digital twin technology, enhancing data processing, model construction, and predictive analysis through advanced algorithms and models [85].

Widespread use of core algorithms

Among the 68 studies included, 64 involved the use of algorithms. Deep learning was mentioned in seven studies, mainly for image segmentation and feature extraction. For instance, Islam et al. [56] applied several deep learning algorithms to classify kidney CT images, while Batchden et al. [57] used convolutional neural networks (CNNs), attention-enhanced CNNs, and recurrent neural networks (RNNs) to detect metastatic diseases from continuous radiological reports and generate metastasis maps. Generative adversarial networks (GANs) were applied in six studies to generate high-resolution imaging data [86, 87], addressing the issue of insufficient rare cancer data [38, 56] and supporting dynamic image generation [88] and surgical navigation [73]. Additionally, four studies used support vector machines (SVMs) for disease classification tasks [54, 58, 89, 90]. Hybrid models integrating cross-domain algorithms provided key support for tumor dynamic simulation and personalized treatment optimization [44, 83, 91].

Multimodal data fusion application

In terms of multimodal data integration for digital twin tumor treatment, 22 studies explored the fusion of multimodal data. For example, Chaudhuri et al. [74] and Gilbertson et al. [20] successfully enhanced tumor treatment model accuracy by combining imaging and physiological data. Wang et al. [84] further combined imaging, omics, and patient characteristic data for virtual patient modeling in immunotherapy. Furthermore, six studies [4, 61, 77, 83, 84, 92]discussed the comprehensive integration of multimodal data, covering a wide range of data fusion methods, though overall research in this area remains limited, indicating that the field is still in the exploratory stage.

Digital twin applications in oncology

Digital twin technology in tumor therapy exhibits multi-layered and synergistic characteristics, covering key application scenarios such as diagnosis, treatment decision-making, prognosis prediction, surgical planning, drug development, virtual trials, tumor microenvironment analysis, and personalized management. Each application scenario incorporates advanced modeling methods and techniques to optimize precise and personalized medical plans. The following sections analyze the functionality, technical features, and specific examples of each application scenario.

To clearly demonstrate the hierarchical structure and functions of these scenarios, Fig. 6 uses a hybrid pyramid diagram and a central radiating mind map to intuitively present the seven application scenarios and their respective functions. The pyramid is divided into three layers: the top layer includes prognosis prediction and treatment decision-making, which directly serve to optimize patient treatment plans through multimodal data integration and dynamic modeling; the middle layer includes diagnosis, surgical planning, and personalized management, which provide support for tumor detection, treatment planning, and patient care across the entire treatment cycle; the bottom layer includes drug development, virtual trials, and tumor microenvironment analysis, reinforcing the overall system with technical support and data foundations.

Diagnosis

In the field of tumor diagnosis, digital twin technology significantly enhances diagnostic accuracy through the integration of multimodal data and deep learning methods, particularly in imaging analysis and early screening. Generative adversarial networks (GANs), as a powerful tool, have shown great potential in medical image processing. Through its generative and discriminative mechanisms, GANs can generate high-quality synthetic medical images, effectively denoising images and reconstructing low-resolution images, especially in tumor early detection. In cervical cancer screening, for instance, GANs achieved an accuracy of 98.91% in classification [88], demonstrating their potential for early tumor detection.

In terms of improving diagnostic accuracy, three-dimensional acoustic modeling technology has also demonstrated unique advantages. Based on the Navier–Stokes equation, this modeling method precisely simulates the propagation behavior of sound waves in soft tissues, providing important evidence for accurate diagnosis and surgical planning of liver diseases [93]. This technology not only enhances diagnostic accuracy but also offers new pathways for early liver disease detection. However, due to its high computational demand, further optimization is required for its clinical application.

The Vision Transformer (ViT) model, a recent advancement, has significantly improved the efficiency of CT image feature extraction due to its attention-based mechanism. In automated detection of kidney tumors and stones, ViT demonstrated superior performance compared to traditional convolutional

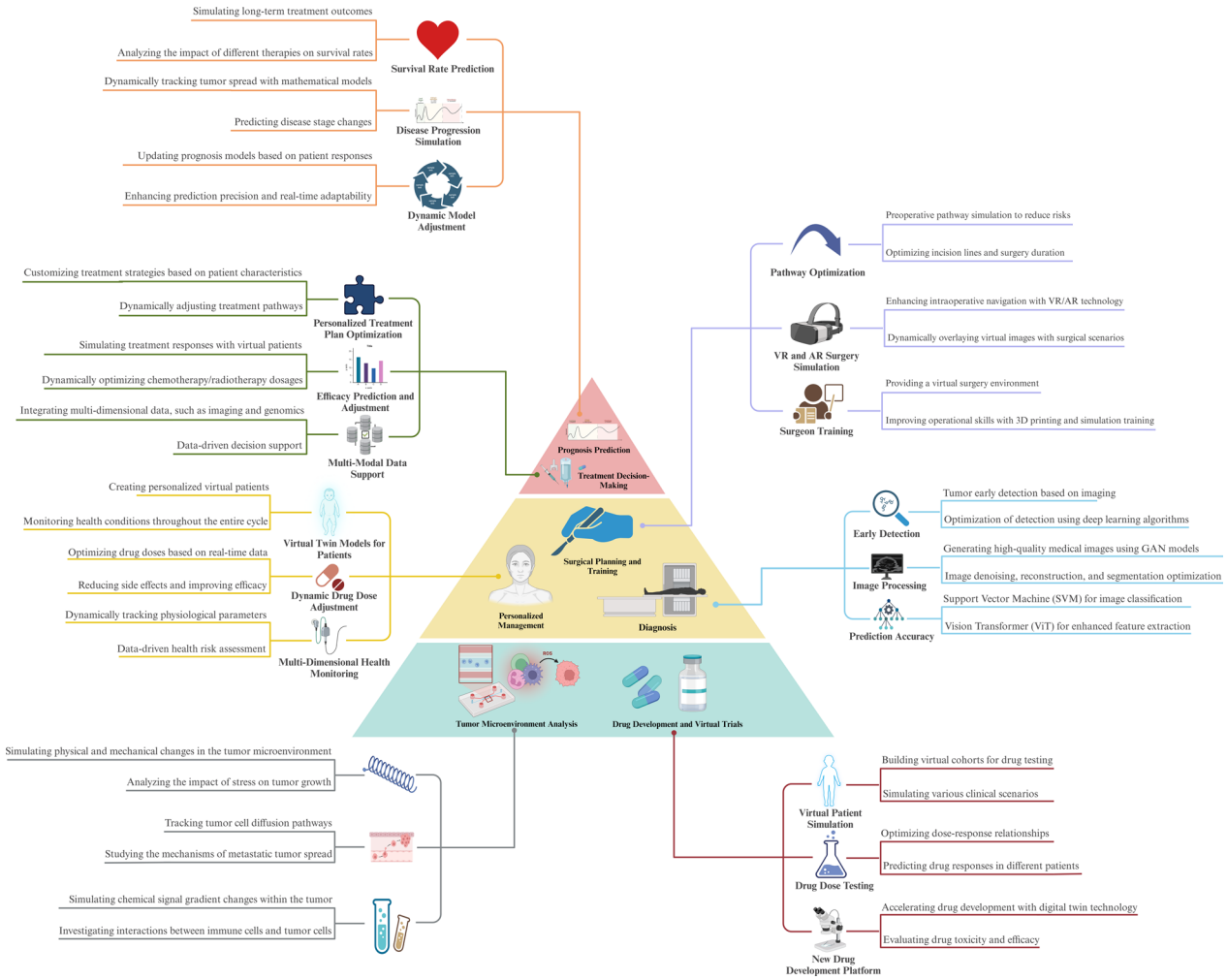

Fig. 6 Hybrid Pyramid Diagram and Central Radiating Mind Map. This figure illustrates the key applications of digital twin technology in oncology, organized into a hierarchical pyramid structure. The top layer focuses on prognosis prediction and treatment decision-making; the middle layer includes diagnosis, surgical planning, and personalized management; and the bottom layer addresses drug development, virtual trials, and tumor microenvironment analysis. These layers integrate data and leverage technological support to collaboratively drive personalized treatment and optimize decision-making processes. These applications rely on advanced technologies such as artificial intelligence, machine learning, and virtual reality (VR) to enhance the precision of cancer treatment. By utilizing digital twin models, they enable the prediction of patient responses, accelerate drug development, and ultimately improve survival rates and quality of life

neural networks, especially in optimizing global information capture and data dependence [56]. However, the complexity of training the ViT model and its high computational resource requirements may pose challenges in real-time applications. Table 2 summarizes the main models, data sources, and research findings in digital twin-based tumor diagnosis, highlighting key advancements.

Personalized management

In tumor personalized management, digital twin technology drives the development of virtual patient models through multimodal data integration and advanced modeling methods. These models precisely simulate patients' physiological characteristics, genomic data, and treatment responses, enabling dynamic adjustments to personalized treatment plans. For instance, a physics-based digital twin model, integrating pharmacokinetics (PK) and pharmacodynamics (PD) models, successfully predicted patients' drug responses under different physiological conditions [41, 61, 96]. This model provided scientific support for optimizing drug treatments, significantly improving individualized treatment outcomes.

Additionally, digital twin technology has shown potential in managing cancer-related chronic pain. By

Table 2 Digital twin models and research progress in tumor diagnosis

Model methods	Data source	Evaluation	Referencess
Deep neural networks	Lung cancer clinical data	Outperformed existing deep learning fault detection models in accuracy and robustness	[37]
Generative adversarial network	Synthetic lung cancer imaging data	Effectively differentiates disease stages (e.g., survival vs. death) and meets medical standards	[55]
Semi-supervised support vector machine	Brain tumor MRI data	Accuracy: 92.52%, Dice Similarity Coefficient: 75.58%	[90]
Fuzzy logic system	Brain tumor MRI data	Dice Similarity Coefficient: 0.936, Jaccard: 0.845,	[69]
Vision transformer	Kidney tumor CT data	Accuracy: 99.3%, F1 Score superior to other models	[56]
Natural language processing	Radiology reports	Multi-report model's Accuracy, Recall, F1 Score higher than single report analysis	[57]
KNN-weighted dual support vector machine	Breast cancer imaging	Outperformed comparison models in Accuracy, Recall, and F1 Score across different datasets	[58]
3D Mesh reconstruction algorithm	Neuroblastoma MRI data	Substantially reduced reconstruction time, providing accurate modeling for neuroblastoma	[4]
K-Means clustering algorithm	Brain tumor MRI data	High efficiency in 3D modeling based on MRI	[70]
Knowledge graph and digital twin model	Multiple myeloma clinical data	Simulated potential treatment strategies, aiding physician treatment assessments	[94]
Classical machine learning models	Breast cancer patient clinical data	Real-time diagnosis and prediction of breast cancer-related indicators	[54]
CervixNet	Cervical cancer cell images	Classification Accuracy: 98.91%	[89]
Navier-Stokes equation modeling	Ultrasound propagation data	Precise simulation of wave propagation, detecting liver lesions	[93]
U-Net network and enhanced deep super-resolution network	Glioblastoma tissue slices	Peak Signal-to-Noise Ratio (PSNR): 31.6 dB, Computation speed: 14 fps	[59]
Hypergraph convolutional network	Kidney tumor CT data	Classification Accuracy: 99.71%, high F1 score	[95]

combining Markov Chain Monte Carlo (MCMC) methods, researchers generated virtual patient populations and simulated the impact of variables like age and gender on fentanyl absorption and efficacy. This approach significantly enhanced the precision of drug dose regulation, avoiding the shortcomings of traditional trial-and-error dosing methods [61]. Furthermore, a physics-driven thermal control model was used to optimize the transdermal fentanyl delivery process, reducing the standard deviation of blood drug concentration by 37.5% [97]. Real-time data analysis platforms, such as Sarconnector®, seamlessly integrate multi-modal data to support continuous optimization of personalized treatment paths, ensuring flexibility in treatment plans [98].

However, one of the main challenges in personalized management is the high complexity of patient physiological and genetic differences, which leads to varying treatment effects among different patients [61, 99]. Furthermore, ensuring the computational efficiency of real-time drug dose adjustments remains a challenge in the practical implementation of these technologies [41, 61, 96]. Table 3 summarizes the main models, data sources, and research findings on digital twin technology in tumor personalized management, showcasing key progress. Figure 7 illustrates the application framework of digital twin technology in tumor personalized management.

Surgical planning and training

In tumor surgical planning and training, digital twin technology leverages various modeling methods and techniques to achieve high-precision surgical simulation and dynamic support. For example, deep convolutional generative adversarial networks (DCGANs) are applied to generate 3D anatomical structures. By combining high-resolution image reconstruction with finite element analysis (FEA), DCGANs simulate the physical responses of bones and soft tissues, especially useful in surgeries like vertebroplasty that require high precision for bone tissue manipulation [86]. This technology not only improves pre-surgical preparation but also offers strong support for intraoperative dynamic adjustments.

Augmented reality (AR) technology combined with dynamic navigation models has further enhanced surgical planning accuracy. By overlaying virtual images onto surgical fields in real time, AR supports dynamic calibration and path planning during surgery, reducing risks and increasing precision [45, 67]. Additionally, advancements in 5G and Internet of Things (IoT) technology have enabled breakthroughs in remote surgical simulation. High-bandwidth, low-latency connections allow real-time remote guidance and training [73].

Virtual reality (VR) combined with 3D modeling has provided innovative tools for surgical training. This

Table 3 Digital twin models and research progress in tumor personalized management

Model Method	Data Source	Evaluation	References
Physics-based Digital Twin Modeling	Virtual patient physiological data and literature data	Reduced average pain intensity by 16%, increased pain-free hours by 23 h over 72 h, significantly improving pain management outcomes	[61]
Multi-purpose Medical Digital Twin (DMT)	Head and neck cancer patient clinical data	Multi-stage patient pathway support system, enhancing decision-making efficiency	[66]
Real-world Time Data Analysis Platform	Sarcoma patient clinical data	Improved treatment flow and patient outcomes, reducing medical costs through multi-disciplinary team comparisons	[60]
Biomedical Data-driven Digital Twin Model	Breast cancer stakeholder interview data	Enhanced personalized treatment, data efficiency, and research potential	[47]
Physiology-driven Digital Twin Model	Real patient data and pharmacokinetics/pharmacodynamics models	Stable drug release, reducing treatment outcome variability	[41]
Physics-based Digital Twin	Virtual patient physiological data and pharmacokinetics simulation	Identified the significant impact of patient weight and age on drug efficacy, optimizing drug delivery strategy to improve pain control	[96]
Thermal Control Drug Release Model	Virtual patient and skin model data	Improved drug delivery stability, advanced peak blood drug concentration by 10.3 h, and reduced pain intensity by 18%	[97]

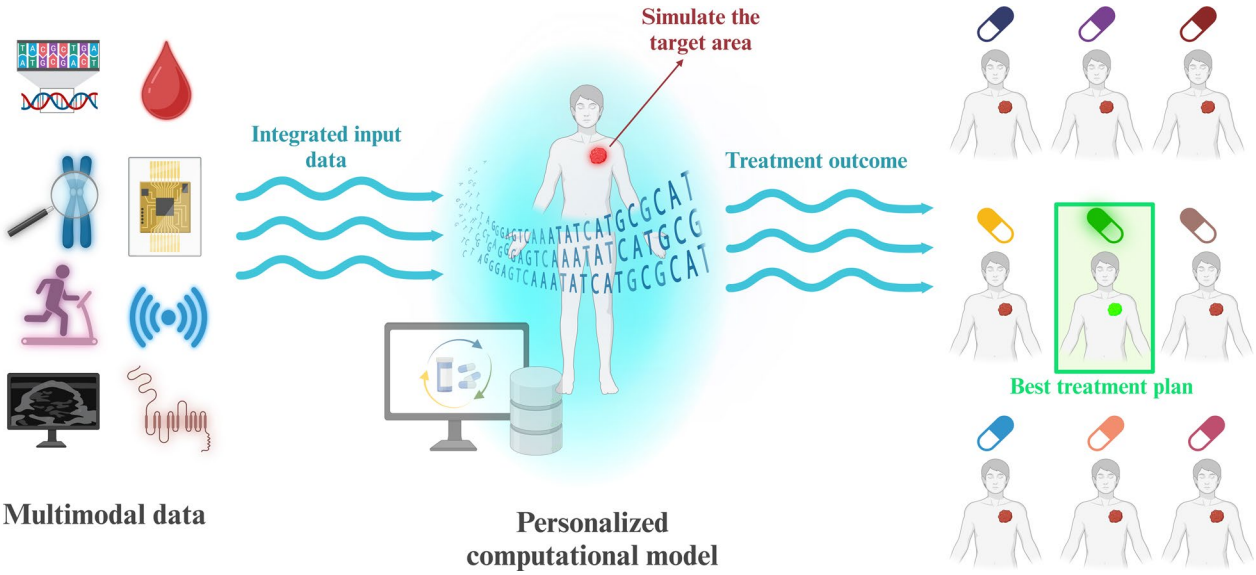

Fig. 7 Digital Twin Application Framework in Tumor Personalized Management. The framework shows how digital twin technology integrates multiple modalities of data, such as genomics, blood biomarkers, behavioral data, sensor monitoring, and imaging data, to construct an individualized virtual model. This model dynamically analyzes how the patient responds to different treatment plans, continuously optimizing the treatment path in real-time

approach builds virtual anatomical and pathological models, offering medical students and junior doctors a risk-free, repeatable environment to practice operations, enhancing their skills and ability to handle emergencies [43]. However, the realism and interactivity of VR still require further research and optimization for different types of surgeries [100]. Table 4 summarizes the detailed model types, data sources, and related research metrics of digital twins in the field of tumor surgical planning and training, highlighting key achievements in current studies. Figure 8 illustrates the application framework of

digital twin technology in tumor surgical planning and training.

Tumor microenvironment analysis

Digital twin technology in tumor microenvironment (TME) analysis employs advanced modeling methods to simulate complex intercellular interactions and dynamic characteristics, providing deeper insights into tumor development and treatment. Multiphase reactive poromechanics models, for instance, describe the interactions among tumor cells, interstitial fluid, and the extracellular matrix. Using such models, Urcun et al. [102] successfully replicated the mechanical environment inside tumors, revealing the relationship between stress distribution and drug diffusion, offering theoretical support for anti-tumor drug development.

Hybrid models combining partial differential equations (PDEs) and ordinary differential equations (ODEs) focus on simulating chemical concentration gradients in the TME, particularly interactions between immune and tumor cells. These models dynamically simulate immune cell migration behaviors, providing critical insights into tumor immunology and optimizing immunotherapy strategies [91].

Cellular automata (CA) models, known for their ability to simulate cell behaviors, are widely used in studying tumor cell migration and metastasis pathways. These models efficiently simulate the diffusion characteristics of tumor cells in the microenvironment and have significant applications in understanding metastasis mechanisms [103]. However, their capacity to capture complex intercellular interactions and heterogeneity needs improvement [104]. Integrating genomic, proteomic, and metabolomic data into hypermodels further extends the application of digital twin technology in TME analysis, providing more accurate support for developing personalized treatment strategies [83]. Table 5 provides a summary of the primary models, data sources, and research outcomes of digital twin applications in tumor microenvironment analysis, highlighting key advancements in the field. Figure 9 illustrates the multi-level application framework of digital twin technology in tumor microenvironment analysis. Relevant references are indicated in the figure legend.

Drug development and virtual trials

In tumor drug development and clinical trials, digital twin (DT) technology enhances personalized treatment by precisely simulating individual biological processes and therapeutic responses. This optimization of drug screening, dose adjustment, and efficacy evaluation accelerates the advancement of tailored therapies. For instance, quantitative systems pharmacology (QSP) models are renowned for their precise prediction of dose–response relationships. By integrating pharmacokinetics with tumor biology, QSP provides a mechanism-driven tool for dose optimization and biomarker identification [77].

Unlike the mechanism-driven nature of QSP models, multi-omics integration models expand the capabilities of tumor microenvironment (TME) modeling by incorporating genomic, proteomic, and metabolomic data. These models are particularly suited for assessing the complex efficacy of immunotherapies [80]. Meanwhile, cellular dynamics simulations explore the behavior of immune cells (e.g., T cells) within the TME, dynamically describing processes such as cell proliferation, differentiation, and apoptosis. This provides valuable data and mechanistic support for optimizing cell therapies [107].

However, individual variability among patients presents challenges to model generalization and personalized dose adjustments [80, 108]. Furthermore, constructing virtual cohorts and ensuring data consistency pose obstacles to the implementation of virtual trials. Variations in efficacy metrics and observation periods across studies can render some data incompatible with virtual trial frameworks, hindering drug development progress [109]. Table 6 summarizes the main models, data sources, and research outcomes of DT technology in tumor drug development and virtual trials, highlighting recent key advancements.

Prognosis prediction

In prognosis prediction, digital twin (DT) technology models individual patient characteristics, dynamically simulating tumor growth and treatment response to forecast therapeutic outcomes and long-term survival rates. Biomathematical models, such as reaction–diffusion equations or partial differential equations (PDEs), are widely used to simulate tumor spread, proliferation, and treatment response [23, 75]. Given the high computational demands of such models, reduced-order modeling (ROM) has been introduced to create representative subsets in low-dimensional spaces, significantly reducing computational requirements and making these models more feasible in resource-limited environments [75].

Simultaneously, machine learning methods have enhanced the accuracy of survival and disease progression predictions by integrating imaging, biomarkers, and clinical data [24, 110]. For example, Salimi et al. introduced the concept of "Organomics," which incorporates radiomic features of healthy organs into prognosis models for non-small cell lung cancer. The study found that

Table 4 Digital twin models and research progress in tumor surgical planning and training

Model method	Data source	Evaluation	References
PD feedback control with newton–euler forward control	Solidworks and Matlab/Simulink simulation data	Average error reduced by 30%, maximum error reduced by 33.3% compared to PD feedback control	[49]
Digital twin with holographic AR	Experimental canine data	Tumor and vascular estimation errors were 2.18 mm and 2.79 mm, respectively; puncture precision was 2.5 mm and 2.17 mm	[45]
Quasi-static unconstrained uniaxial compression test and continuum mechanics constitutive model	Fresh porcine thyroid tissue	Constructed a hyperelastic constitutive model describing quasi-static mechanical performance	[46]
rAC-GAN with digital twin and 5G cloud support	Lung cancer patient clinical data	AUC reached 0.92 and 0.93, predictive performance consistent with epidemiological statistics	[73]
ReconGAN and finite element model	Spine metastasis patient clinical data	Evaluated post-vertebroplasty mechanical stability and cement morphology	[86]
ReconGAN and finite element method (FEM), deep learning	Micro-CT images and clinical data	Achieved digital twin reconstruction of vertebrae and fracture risk prediction	[87]
Machine learning-optimized digital twin with cryosurgery modeling	Cryoprobe experimental data	Achieved precise cryotherapy, optimized cooling modes to reduce healthy tissue damage	[101]
Augmented reality (AR)	Head and neck tumor CT data	Optimized surgical pathways for head and neck tumors, improving intraoperative safety and precision	[67]
Digital twin computational model and image-guided microwave ablation simulation	Liver cancer imaging data	Predicted that increased fat content led to a 29%–60% increase in ablation volume, enhancing prediction accuracy	[42]
Metaverse combined with 3D virtual model	3D reconstructed anatomical data of patients	Provided an immersive surgical planning experience, overcoming spatial distance limitations	[43]
Mixed reality combined with 3D-printed brain tumor resection training model	Brain tumor imaging data	Offered a complete training process from surgical planning to execution, improving neurosurgical skill training	[44]
2½D point cloud registration method based on digital twin	Tissue scan data from pig head specimens	Precisely quantified tissue volume changes due to temperature variation, suitable for assessing tissue deformation in head and neck tumor resection surgeries	[50]
Patient-specific 3D computational fluid dynamics (CFD) model	Liver cancer patient CT data	Grid simplification reduced computation time by 45% while maintaining tumor dose prediction error below 1.4%, demonstrating reliable sensitivity analysis	[92]

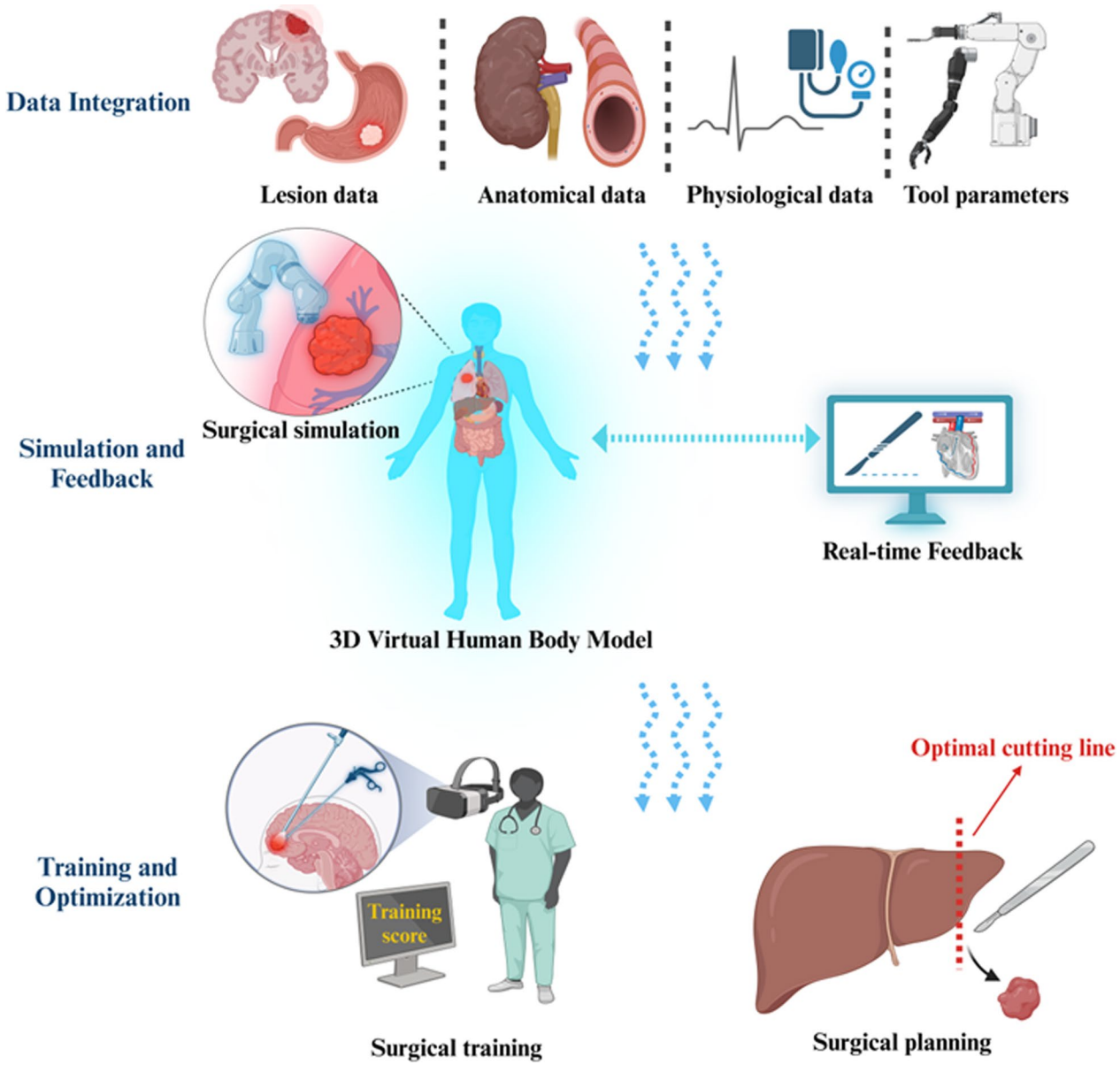

Fig. 8 Digital Twin Application Framework in Tumor Surgical Planning and Training. The framework integrates lesion data, anatomical data, physiological data, and surgical tool parameters to construct 3D virtual models. Surgeons use virtual reality devices for surgical planning and training, receiving system-optimized cutting lines and performance scores to improve precision and skill level

integrating healthy organ data significantly improved the predictive accuracy of machine learning models compared to using tumor data alone [110]. This approach provides a more holistic perspective on tumor prognosis prediction and highlights the advantages of DT technology in multi-modal data integration.

Additionally, network science models, such as SynTwin, leverage graph structures to connect data from similar patients, generating virtual patient profiles. This enhances the applicability and generalizability of models across diverse clinical scenarios [76]. Table 7 summarizes the main models, data sources, and research outcomes of DT technology in tumor prognosis prediction, showcasing recent key advancements.

Treatment decision-making

Digital twin (DT) technology in tumor treatment decision-making focuses on dynamic modeling and personalized optimization. A key approach is the Deep

Table 5 Digital twin models and research progress in tumor microenvironment analysis

Model method	Data source	Evaluation	References
Multiphase reactive poromechanics model	Tumor organoid experimental data	Revealed key mechanisms linking stress to tumor cell phenotype changes	[102]
Hybrid PDE-ODE immune-tumor chip model	Microfluidic cancer chip data	Simulated immune cell migration and verified chemical signal effects on immune-tumor interactions	[91]
Electrophysiological digital twin model for A549 lung cancer cells	Experimental and simulated membrane potential data of A549 cells	Predicts the effects of ion channel regulation on the cell cycle, revealing critical links between abnormal membrane potential and cancer progression	[81]
High-performance computing (HPC)-supported multiscale agent-based model	Simulated data from cell signaling and physical models	Simulates up to millions of cells with real-time user interaction, enhancing understanding of cancer cell signaling and physical behavior	[105]
Cell migration model based on cellular automata	Wound healing experiments and in vitro tumor cell data	Develops power-law equations describing wound healing and cell migration, providing a robust tool for evaluating cancer cell migration and anti-invasive therapies	[103]
Cell-state transition model (cSTAR)	Single-cell phosphoproteomics data	Identifies core signaling networks in breast cancer cell states and predicts novel drug targets for modulating cell-state transitions	[106]
Multidisciplinary hypermodel framework	Genomic, imaging, and clinical data of tumor patients	Integrates cellular metabolism, signaling pathways, and biomechanical models to predict tumor response to radiotherapy and the relationship between post-chemotherapy proliferation and therapeutic outcomes	[83]

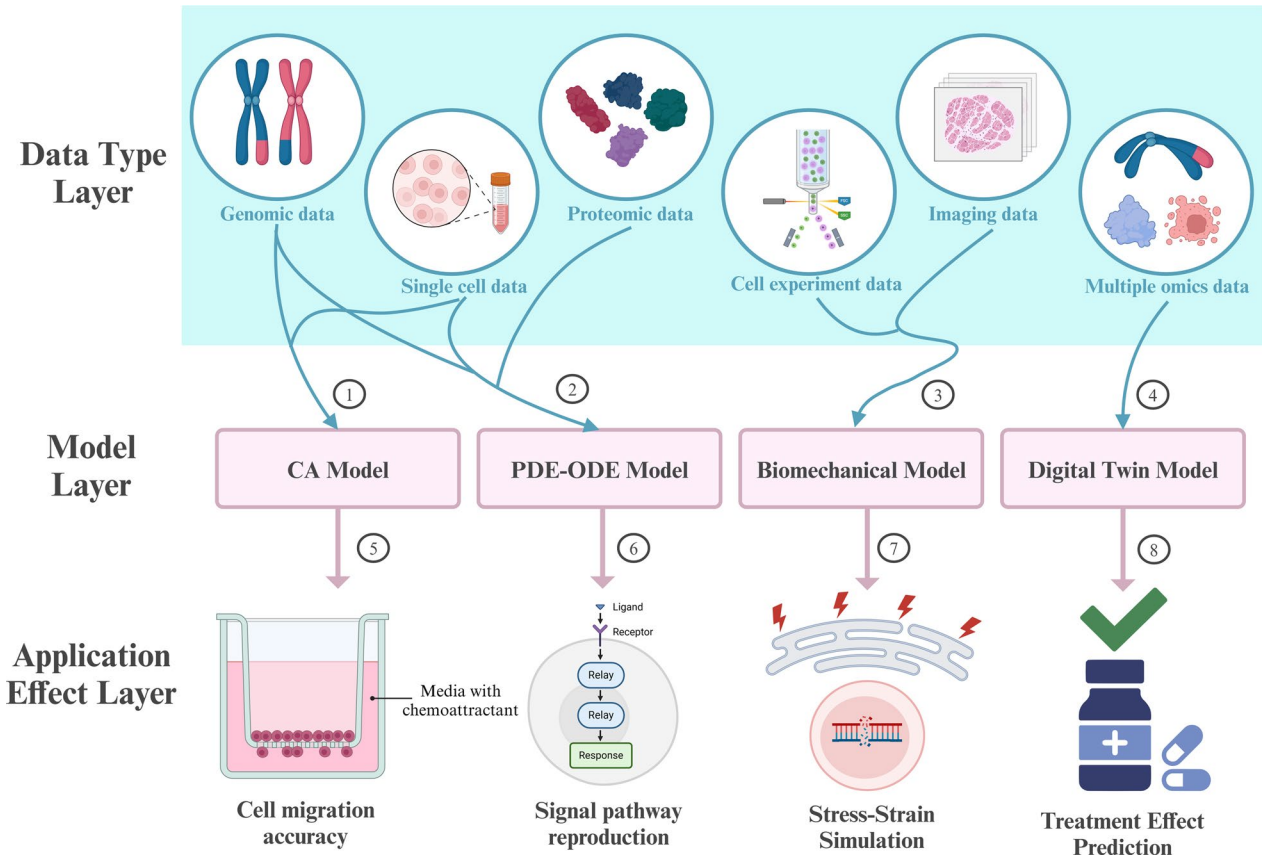

Fig. 9 Multi-Layer Framework of Digital Twin Technology in Tumor Microenvironment Analysis. This framework integrates data types such as genomics, single-cell analysis, proteomics, and biomechanics into models like CA, PDE-ODE, and hypermodels. Applications include signal pathway reconstruction, stress simulation, and treatment outcome prediction. References: Arrow ① is derived from reference [103]. Arrow ② is derived from references [91, 106]. Arrow ③is derived from references [83, 102]. Arrow ④ is derived from reference [83]. Arrow ⑤ is derived from reference [103]. Arrow ⑥ is derived from reference [91]. Arrow ⑦ is derived from references [83, 102]. Arrow ⑧ is derived from reference [83]

Table 6 Digital twin models and research progress in tumor drug development and virtual trials

Model method	Data source	Effect evaluation	References
GAN-based synthetic data model	Clinical data of lung cancer patients	Validated with statistical hypothesis testing (goodness-of-fit) and expert oncologist reviews	[72]
QSP digital twin system	Clinical trial data for NHL patients treated with mosunetuzumab	Exposure–response predictions and identification of predictive biomarkers; validated against clinical observations	[77]
Digital twin for cGvHD patients	Real-world clinical trial data from Phesi's Trial Accelerator™ database	Validation of SOC arm efficacy against literature benchmarks for response rates	[109]
Multi-omics QSP model	Multi-omics datasets of tumor microenvironment	QSP model accuracy validated using clinical trial outcomes and biomarker predictions	[80]
NeoAgDT for vaccine optimization	RNA sequencing and mutation data from public datasets	Improved recall of neoantigen selection compared to traditional ranking-based approaches	[79]
TCR-engineered cell therapy model	Clinical trial data for HPV-associated cancer patients	Kinetics predictions matched clinical data, with Tscm enrichment shown to improve therapeutic persistence	[107]
QSP-IO with agent-based models	Multi-omics and clinical trial data	Validated using retrospective analyses and predictions for response to immune checkpoint inhibitors	[84]

Table 7 Digital twin models and research progress in tumor prognosis prediction

Model method	Data source	Effect evaluation	References
MRI-based digital model	MRI and dynamic contrast-enhanced MRI data from triple-negative breast cancer patients	Achieved AUC of 0.89 for predicting therapy response, superior to standard metrics	[23]
ML-based digital twin system	Clinical data warehouse for prostate cancer patients	Biochemical recurrence prediction accuracy up to 96.25% using machine learning	[24]
Virtual clinical trial simulator	Non-small cell lung cancer patients with pembrolizumab therapy	Predicted progression-free survival effectively, suggesting treatment beyond progression	[111]
Graph-based SynTwin model	Cancer registry data from SEER (n = 87,674)	Improved AUROC from 0.791 to 0.864 using synthetic patient data for mortality prediction	[76]
Reduced order PDE model	MRI-based tumor data for triple-negative breast cancer	Reduced computational time by 378 × with high concordance in predictive accuracy	[75]
PET/CT organomics model	Radiomics from PET/CT imaging of non-small cell lung cancer patients	Integration of healthy organ data improved survival prediction (C-index = 0.68)	[110]
Target trial emulation framework	Real-world sarcoma patient data	Highlighted risks of unplanned resections affecting recurrence-free survival	[40]
UMAP-based digital twin workflow	Breast cancer data from The Cancer Genome Atlas (TCGA-BRCA)	Identified patient subgroups with high similarity; improved survival prediction and treatment stratification	[52]

Q-Learning (DQL) model, which uses a reinforcement learning framework to simulate multi-step interactions between physicians and patients, predicting optimal treatment pathways. By inputting extensive historical treatment data, the DQL model creates a learning system that dynamically optimizes chemo-radiotherapy regimens to meet the specific treatment needs of individual patients [65]. Notably, Bayesian optimization frameworks excel in handling uncertainties, particularly in designing personalized radiotherapy plans for high-grade gliomas. By probabilistically modeling longitudinal MRI data, Bayesian optimization generates tailored treatment plans while balancing efficacy and toxicity. This approach not only enhances treatment outcomes but also reduces damage to normal tissues [11].

Mathematical models have also played a critical role in optimizing chemotherapy regimens for acute myeloid leukemia (AML). By analyzing white blood cell counts, drug metabolism parameters, and patient toxicity thresholds, these models simulate the physiological impact of different treatment strategies. Through systems of equations describing pharmacokinetics (PK) and pharmacodynamics (PD), mathematical models provide scientific evidence for optimizing chemotherapy doses and timing [53].

Furthermore, multi-modal data integration is indispensable in treatment decision-making with DT technology. For instance, DT-enabled visualization platforms such as the myCMIE system integrate patients' molecular profiles, genomic data, and clinical records to generate personalized treatment recommendations in real time. Compared to traditional methods, the myCMIE system offers a comprehensive perspective by deeply integrating various data types, enabling treatment plans that better align with individual patient needs [61]. Table 8 the primary models, data sources, and research outcomes of DT technology in tumor treatment decision-making, showcasing recent advances.

Discussion

This study systematically explores the innovative applications of digital twin (DT) technology in tumor therapy, analyzing its current state, research trends, and key challenges while proposing future directions. Using bibliometric analysis and a scoping review, the rapid growth of DT applications in oncology since 2020 was revealed, particularly in leading countries such as the United States, Germany, Switzerland, and China.

The United States' prominent publication output underscores its pivotal role in advancing the integration of digital twin technology with cancer treatment. Germany and Switzerland follow closely, reflecting Europe's robust growth in this area. Notably, large-scale initiatives such as the European Union–funded Ecosystem Digital Twins in Health (EDITH) project [112] and the Swedish Digital Twin Consortium [113] are driving significant progress in the application and innovation of digital twin technology across Europe. China has made substantial research contributions, highlighting its sustained focus and active participation in this field.

Moreover, international collaboration has become increasingly close, particularly between the United States, European countries, and China. This cross-border cooperation has facilitated the rapid development of the technology, especially through synergies in data sharing, standardization of technologies, and global clinical trials,

Table 8 Digital twin models and research progress in tumor treatment decision-making

Model method	Data source	Effect evaluation	References
Deep Q-Learning (DQL) with patient digital twin model	Clinical data from patients with oropharyngeal squamous cell carcinoma	Achieved an average prediction accuracy of 87.35%, improved survival rates by 3.73%, and reduced swallowing difficulty rates by 0.75%, supporting optim	[65]
myCMIE molecular information exchange system	Patient Molecular Profile (MPR) data	Facilitated the integration of molecular information, building a molecular digital twin community for enhanced understanding and discussion of personalized treatment	[51]
Uncertainty-based predictive digital twin model	MRI imaging and clinical data from high-grade glioma patients	Personalized radiotherapy plans increased tumor progression-free time by 6 days or reduced radiation dose by 16.7% (10 Gy) at the same control level	[11]
Digital twin with mathematical modeling	Clinical data from AML patients	The AC-123 regimen reduced white blood cell recovery time (improved in 99.6% of simulations) without increasing leukemia relapse risk compared to AC-135	[53]
DITTO Visualized digital twin model with reinforcement learning	Treatment data from head and neck cancer patients	Provided personalized treatment risk assessment and optimized decision support, enhancing interpretability and clinical credibility	[68]

which will accelerate the application of digital twin technology in cancer treatment. As international cooperation deepens, the global prospects for the application of digital twin technology in oncology continue to expand.

The analysis of funding sources reveals that government agencies, particularly the U.S. National Institutes of Health (NIH), play a leading role in advancing research on digital twin technology in the oncology field. Among the top eight funding institutions, apart from those in the United States and Switzerland, only China's National Natural Science Foundation provided three instances of funding. This highlights a certain degree of imbalance in the global funding landscape for digital twin research in oncology. Additionally, in October 2024, the National Science Foundation (NSF), the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA) jointly launched the Biomedical Digital Twin Technology Innovation Program (FDT-BioTech), providing over $6 million in funding for 7 projects, further demonstrating the U.S. government's leading role in the field of digital twin technology and its continued support in advancing technological development [114].

In terms of funding structure, government support accounts for 52.88% of the total funding instances, followed by universities and research institutions at 18.27%, while corporate and private funding represent a relatively small share. This indicates that current research heavily relies on public funding, with government support ensuring a degree of independence and the sustained development of fundamental science. However, the limited contributions from corporations and private sponsors may hinder the commercialization and clinical translation of research outcomes [115]. Future efforts should focus on strengthening public–private partnerships, attracting more corporate investment, and fostering deeper integration between research and application.

Additionally, the average number of funding sources per study is 2.12, but government-funded projects average only 1.53 sources, slightly below the overall mean. This suggests that current research funding is relatively dispersed, potentially requiring higher levels of coordination and focused investment to address key challenges in digital twin technology for oncology, such as data standardization and interdisciplinary collaboration [116]. Swiss foundations (e.g., OPO Foundation, Margrit Weisheit Foundation) have shown consistent support in this field, providing critical backing for long-term research and innovative exploration. This model offers a valuable reference for other countries and regions: establishing dedicated funds to encourage free exploration and high-risk, high-reward research may be a viable strategy.

Overall, although the funding landscape is diverse, it remains predominantly driven by government support. Issues of regional disparity and insufficient investment in applied research remain significant. Future progress may depend on fostering international collaboration, integrating academia and industry, and establishing dedicated funds to accelerate the global development and clinical translation of digital twin technology.

Key findings and significance

This study reveals the diversity and application trends of digital twin (DT) technology in the oncology field through an analysis of sample size distribution. The results demonstrate significant variation in sample sizes across studies, ranging from a few cases to tens of thousands of patients. This phenomenon reflects the dual development trajectory of DT technology in oncology: While emphasizing robustness and universality in large-scale clinical applications, equal importance is placed on achieving technological innovation and breakthroughs in specialized fields.

Firstly, studies with small sample sizes (< 50 cases) primarily focus on technology validation and early development stages, relying on clinical trial data, medical imaging data, and animal model data. These studies lay the foundation for personalized treatment and precision testing of DT technology. However, the limited sample size may constrain the generalizability of these findings, failing to fully address the clinical needs of broader populations. Future research should aim to expand sample sizes and conduct multi-center, long-term clinical trials to validate the widespread applicability of DT technology.

Secondly, studies with large sample sizes (> 500 cases) showcase the broad potential of DT technology in areas such as tumor diagnosis and personalized management. These studies leverage multi-center databases and large-scale datasets, ensuring the representativeness of results and the generalizability of clinical applications. The high clinical translation potential of large-sample studies makes them pivotal in DT research, particularly in widely studied tumor types like lung and breast cancer.

From the perspective of data sources and application scenarios, medical imaging and clinical data dominate in diagnostic and treatment decision-making contexts, while virtual patient data and laboratory data are predominantly used for technology validation and personalized management. The Sankey bubble chart illustrates the flow and role of these data types in tumor research, providing a clear direction for future studies. Additionally, the relationship between sample size and tumor type is noteworthy. Breast and lung cancers feature prominently in DT research with large sample sizes, reflecting the broad clinical demand and research focus on these tumors. Conversely, brain tumors and certain specific subtypes are more often studied with small sample sizes,

focusing on precision medicine and micro-mechanism exploration. This differentiation highlights the tailored application of DT technology across various tumor types.

In summary, the diversity in sample size distribution and data sources underscores the broad application potential and ongoing challenges of DT technology in oncology. Future research should prioritize the integration of large-sample, multi-center data while improving reporting standards and transparency to advance the clinical application and widespread adoption of DT technology.

Furthermore, this study systematically analyzes the data processing and artificial intelligence (AI) applications in tumor treatment using DT technology. Clinical and genomic multi-source data provide a realistic foundation for model construction, while AI algorithms play a core role in data processing, dynamic modeling, and multimodal integration. Multi-omics analysis enhances the models' adaptability to individual differences. This synergy between technologies not only facilitates innovative applications but also establishes a solid foundation for achieving precision oncology [17]. For example, a DT-based classification system grounded in systems and mathematical modeling theories [21] and a DT framework for predicting cancer progression in prostate cancer patients [24] both demonstrate the critical significance of data-driven approaches and algorithmic integration in improving model performance and clinical applications.

Our study demonstrates that multi-omics data play an indispensable role in constructing digital twin tumor models while simultaneously exposing several pressing challenges. Specifically, genomic data play a pivotal role in relevant applications by capturing driver gene mutations, which provide a robust foundation for personalized treatment and targeted therapies [117]. Meanwhile, although proteomic and metabolomic data have been explored in seven studies to elucidate signaling pathways and metabolic reprogramming within tumor cells, their integration remains insufficient. The heterogeneity of the data and the lack of standardized protocols limit their potential in the detailed analysis of the tumor microenvironment and treatment response predictions [118]. Therefore, improving data preprocessing and integration methods will be a key focus for future work.

Additionally, although single-cell omics currently represent only about 5.71% of the field, they offer unique advantages in revealing tumor cell heterogeneity and dynamic changes in the immune microenvironment [119]. For example, the single-cell electrophysiological model developed by Baumgartner et al. [81] provides a novel perspective for capturing micro immune responses, suggesting that this data type could be further expanded for clinical evaluation in the future.

Overall, multi-omics data offer multidimensional support for digital twin models, enhancing their ability to simulate tumor biological characteristics and guide personalized treatment. However, challenges such as data standardization, heterogeneity handling, and integration algorithms remain urgent issues that need to be addressed.

Comparison with existing studies

As a scoping review, this study systematically examines the current applications, research trends, and major challenges of digital twin (DT) technology in tumor therapy. Compared with existing review articles, this study presents several notable innovations and advantages:

Firstly, Most existing reviews focus on the broad application of DT technology in healthcare or specific tumor types. For instance, Katsoulakis et al. reviewed the potential and challenges of DT technology in healthcare [120], while Fuchs et al. discussed how digital health technologies and AI promote value-based precision sarcoma care [121]. However, reviews specifically addressing the overall application of DT technology in oncology, encompassing multiple tumor types and application scenarios, remain limited. This study fills that gap by providing a comprehensive overview of DT applications across a wide range of tumor types and scenarios.

Secondly, This study offers an in-depth analysis of sample sizes and data sources, revealing application trends, research disparities, and future development directions for DT technology in oncology. Existing reviews often lack such detailed examinations, particularly concerning the relationship between sample size distribution, data sources, and application scenarios.

Additionally, Through a systematic review of medical imaging data, multi-omics data integration, and advanced AI algorithms, this study highlights the precise applications of DT technology in tumor therapy. We summarizes the models, technical challenges, and advancements across various application scenarios, including diagnosis, treatment decision-making, prognosis prediction, surgical planning, drug development, virtual trials, tumor microenvironment analysis, and personalized management. This multi-layered and multidimensional analytical perspective provides a richer understanding of DT applications in oncology compared to existing reviews.

Finally, by incorporating bibliometric analysis, this study uncovers the global research distribution and funding models of DT technology in oncology. It identifies the rapid growth of DT research and highlights differences in funding support and international collaboration among countries and regions. This global perspective offers new insights into the dynamics of DT technology development. In contrast, existing reviews often lack systematic

analyses of global research distribution and funding models, limiting their ability to reflect the role of international collaboration and funding in driving technological advancements.

In conclusion, Through the exploration of sample size distribution, data processing and integration, and global research dynamics, this study addresses the limitations in comprehensiveness and detail found in existing reviews. It provides a more systematic and complete picture of the applications of DT technology in tumor therapy. This contribution not only helps the academic community better understand the current state and future trends of DT technology but also offers scientific evidence and guidance for implementing precision oncology in clinical practice.

Challenges

Global challenges of data diversity and sample size insufficiency

Current status and issues Current research indicates that the development of digital twin (DT) technology heavily depends on the diversity and adequacy of data samples [122]. However, sample size analysis in this study reveals significant imbalances in tumor-related datasets. Large sample data are primarily concentrated in common cancers such as lung and breast cancer, while rare tumors (e.g., high-grade gliomas) suffer from severe data scarcity. Furthermore, discrepancies in distribution and quality among different data sources (e.g., imaging, omics, and clinical records) limit the generalizability and reliability of DT models [17].

Analysis and recommendations To address the limitations in model generalization caused by insufficient sample sizes, previous studies have proposed expanding data representativeness through multi-center collaborations. For example, some studies integrated data from multi-center clinical trials and real-world datasets to construct virtual patient cohorts, successfully simulating disease diversity and the effects of various treatments [39, 109]. Other research has utilized generative adversarial networks (GANs) and DT models to merge heterogeneous data from multiple medical centers, thereby enhancing model robustness and predictive capability [24, 73].

Notably, Virtual patient technology has also emerged as a promising approach to extend real patient datasets. This method evaluates the effectiveness of complex treatment strategies by simulating diverse clinical scenarios, significantly improving model validation efficiency. However, uncertainties in input parameters and potential differences between simulated physiological responses and real patients may affect result reliability [123]. To address this, an increasing number of studies have combined real patient data with multi-omics information (e.g., genomic and imaging data) to calibrate virtual patient models, improving their credibility and clinical relevance [80, 84]. Additionally, multi-modal data integration based on DT technology has proven effective in overcoming challenges associated with data heterogeneity and diversity. For instance, Moztarzadeh et al. [64] proposed a DT framework that integrates machine learning and metaverse technologies to construct real-time digital replicas of patients, improving diagnostic and treatment precision and providing new avenues for rare disease research. Similarly, Keller et al. [66] developed a Digital Medical Twin (DMT) platform that supports personalized treatment for complex diseases by integrating and dynamically invoking multi-modal data, offering a feasible framework for multi-center collaboration in rare disease research. At a higher level, the American Society of Clinical Oncology's subsidiary, CancerLinQ, developed a global large-scale data integration platform that aggregates extensive cancer patient data to guide optimal treatment and improve clinical outcomes [124]. CancerLinQ's success highlights the critical role of large-scale data integration in enhancing DT model performance and the profound impact of institution-driven data utilization models on the industry.

Barriers to technical integration

Current Status and Issues While DT technology demonstrates significant potential in data processing and AI applications for tumor therapy, the comprehensive integration of multi-modal data remains a major challenge [66, 94, 125]. Only a limited number of studies [4, 61, 77, 83, 84, 92] have achieved full integration of multi-modal data, primarily due to two major challenges in interdisciplinary collaboration:

1. Insufficient standardization of different data types (e.g., imaging, genomics, and biomechanical information), which severely restricts cross-platform collaboration [126].
2. The scarcity and incompleteness of available multi-modal data, further hindering the efficient integration of patient-specific information [127].

Moreover, current research tends to focus on genomic and proteomic analyses, while metabolomics and single-cell omics integration remain underutilized. This not only limits the biological depth of modeling but also restricts the full potential of multi-modal integration. Additionally, most studies prioritize optimization within single

domains, lacking a comprehensive cross-domain integration framework.

Analysis and recommendations To overcome these barriers, future research should prioritize the integration of metabolomics and single-cell omics data to enhance the biological depth of models, providing multi-dimensional support for precise modeling in tumor therapy. Several innovative tools and frameworks have already demonstrated the potential for technical integration. For example, Xu and Kowalski [51] developed an interactive platform that integrates known and unknown genetic variations to create a comprehensive "total molecular profile," significantly improving data-sharing efficiency and optimizing multi-modal data integration processes. Similarly, Sainz-DeMena et al. [4] developed the im2mesh tool, which combines medical imaging, AI, and engineering modeling to automatically generate personalized 3D network meshes. This tool not only enhances the efficiency of transitioning from imaging to DT model construction but also offers a modular design with high interoperability, providing a concrete solution for complex diseases such as tumor microenvironment modeling. Merchant et al. [105] proposed a framework to address delays and synchronization issues in large-scale parallel simulations, enabling dynamic behavior modeling and real-time interactive exploration of complex systems.

Beyond these technical advances, addressing integration challenges requires robust public–private partnerships and international research alliances to promote standardization. In the near future, global digital twin alliances—bringing together industry, government, academia, and practitioners—will be essential for standardizing digital twin methodologies and establishing interoperability protocols. Initiatives such as the Swedish Digital Twin Alliance [113], the DigitWins Alliance [128], and the broader Digital Twin Alliance® [129] exemplify how collaborative networks can foster shared standards and accelerate cross-domain integration.

Moreover, developing a universal digital twin design and development platform is crucial. Early steps in this direction are evidenced by initiatives like Boeing's virtual shared workspace, which creates a global collaborative environment to harmonize practices among industry partners [116].

Privacy and ethical challenges

Current status and issues The application of DT technology in oncology involves highly sensitive patient data, such as genomic and imaging data [130], making privacy protection and the lawful use of data critical ethical challenges [131]. Furthermore, the fairness and transparency of existing algorithms across different populations remain unresolved [132]. Hernandez-Boussard et al. [9] noted that Cancer Patient Digital Twins (CPDT) are susceptible to biases when learning from skewed datasets, reflecting systemic inequities in existing healthcare systems.

Analysis and recommendations Existing studies indicate that GANs can effectively anonymize sensitive patient data by generating synthetic datasets, which not only protect privacy but also expand data availability in data-scarce areas [55, 72, 73]. Similarly, federated learning-based models improve algorithm performance by mitigating risks associated with centralized data sharing [133]. In addition to these techniques, adopting robust privacy-by-design practices—such as strong encryption, secure transmission protocols (e.g., HTTPS or VPN), and regular anomaly detection—can further safeguard sensitive information [134]. Integrating blockchain technology into DT systems also offers a promising means of enhancing data integrity and transparency by enabling decentralized consent management and efficient auditing. Moreover, addressing system-level vulnerabilities, as demonstrated by Zhang et al. [37] with models that capture bidirectional contextual relationships in IoT environments, can mitigate risks like model manipulation. On the ethical front, frameworks such as that proposed by Moztarzadeh et al. [64], which build real-time, reliable cancer DT models, not only optimize diagnostic and treatment decisions but also reduce inherent biases in clinical applications. For a broader regulatory context, readers may also consult initiatives like the EDITH project's Strategic Plan, which outlines comprehensive guidelines on data collection, privacy, and ethical standards for deploying DT technology in healthcare [112].

Challenges in clinical translation and applicability

Current status and issues Although DT technology shows remarkable potential in experimental studies, its translation from lab to clinic faces numerous challenges. High computational complexity and hardware requirements hinder its adoption in small and medium-sized healthcare institutions [135–137]. Additionally, the transition of complex models to clinical applications demands extremely high reliability and robustness [138, 139]. The lack of interpretability in current models undermines trust from clinicians and patients, impacting their practical application in clinical decision-making [140, 141]. Most research remains in experimental stages, with insufficient external validation and cross-institutional application, raising concerns about the reliability and generalizability of models in real-world clinical settings [23, 40].

Analysis and recommendations To address resource constraints in clinical settings, Merchant et al. [61] pro-

posed the use of high-performance computing (HPC) for large-scale agent-based simulations, optimizing distributed computation for real-time interaction. Christenson et al. [75] demonstrated that simplified modeling techniques, such as proper orthogonal decomposition (POD), reduce computational demands, offering solutions for low-resource environments. Lorenzo et al. [138] emphasized the need to quantify numerical approximations and uncertainties in tumor growth modeling to enhance model robustness and generalizability. Wentzel et al. [68] developed the DITTO platform to improve model interpretability. By incorporating visual tools such as time-risk curves, feature contribution analysis, and patient comparisons, DITTO significantly enhances the transparency of model predictions and clinical trust. This approach provides valuable references for promoting DT technology in clinical practice, particularly in building trust and improving model applicability.

Limitations of the study

Despite providing a comprehensive analysis, this study has several limitations. First, the exclusive use of English-language sources may have underestimated the breadth of relevant literature in this field. Second, the inclusion of studies relied on subjective judgment by the researchers, which could introduce selection bias. Additionally, as the application of digital twin (DT) technology in tumor therapy remains in its early stages, the limited number of related studies may affect the comprehensiveness and representativeness of the analysis. Lastly, the pragmatic approach to identifying studies explicitly labeled as "digital twin" might have excluded relevant papers describing predictive models without explicitly using this term, potentially underestimating the scope of published literature on DT applications in oncology.

Future research directions

Based on the findings of this study, future research should prioritize the following areas:

1. Data Diversity and Shared Platforms

Through international multi-center collaboration, a diverse and high-quality tumor data-sharing platform can be established to ensure the representativeness and adaptability of sample distributions. This not only enhances the generalization capability of digital twin models but also fosters technological exchange and collaboration between different countries and regions [142]. For example, a global tumor data repository could be developed to integrate clinical trial data and real-world data from various countries, supporting broader model training and validation.

2. Standardization of Tools and Frameworks

To address the challenges of technical integration, future research should focus on driving the standardization of technical tools and data frameworks, particularly in unifying data formats, interface standards, and validation methods. This will improve the efficiency of multimodal data integration, provide more accurate support for model validation, and resolve the fragmentation of imaging, omics, and dynamic physiological data, thereby enhancing the applicability and comparability of digital twin technology. Furthermore, developing highly interoperable platforms is critical for promoting interdisciplinary and cross-institutional collaboration, as it will help accelerate the development of standardized technical methods and interoperability protocols, especially for the global implementation of digital twin technology. Strengthening public–private partnerships will not only drive the implementation of these standards but also foster cross-domain collaboration, ensuring the effective integration of technical tools in complex issues like tumor treatment.

3. Data Privacy and Ethical Standards

Strengthen research on data privacy protection and ethical standards to ensure the lawful use and privacy protection of patient data during the application of digital twin technology. Building on current practices, future efforts should focus on refining privacy-by-design strategies, including robust encryption, secure transmission, and blockchain-enabled consent management. Additionally, developing mechanisms to address data biases, enhance algorithmic transparency, and ensure equitable representation across diverse patient populations will be essential. Research should also explore ways to integrate real-time ethical decision-making frameworks into DT systems to further align with evolving healthcare regulations and maintain patient trust.

4. Clinical translation and validation

Accelerating the clinical translation of DT technology requires multi-center clinical trials to validate the applicability and reliability of models. Large-scale trials should test the efficacy and utility of DT models across different tumor types and treatment stages. Enhancing the training of clinicians and technical staff will improve their ability to integrate DT technology into clinical practice [143]. Meanwhile, developing user-friendly tools with

intuitive interfaces will enable non-technical users (e.g., clinicians) to adopt these technologies more easily. Additionally, Regulatory bodies such as the FDA (U.S.) and EMA (Europe) must also establish clear guidelines for using DT technology in clinical trials [144].

5. Optimization of virtual patient modeling

Future advancements should focus on developing virtual patient modeling technologies with higher biological fidelity to better reflect the complex physiological states of patients. Meanwhile, optimize multimodal data integration methods to enhance the accuracy and real-time performance of the model.

Conclusion

Digital twin technology demonstrates immense potential in tumor therapy by optimizing personalized treatment plans through multi-modal data integration and dynamic modeling. However, challenges such as insufficient data diversity, imbalanced sample sizes, limited interoperability of technical frameworks, and issues related to data privacy and ethics remain unresolved. Future efforts should focus on fostering international collaboration, building data-sharing platforms, standardizing cross-disciplinary frameworks, and strengthening ethical guidelines to promote the widespread application of DT technology in precision oncology. These measures will improve treatment outcomes and the quality of life for patients.

As technology advances and research deepens, DT technology has the potential to transition from the "virtual" to the "real," becoming a critical tool in precision medicine and contributing to the global fight against cancer. This study provides a systematic analysis of DT applications in tumor therapy, offering a comprehensive perspective and outlining directions for future research. It is hoped that this study will attract academic attention and facilitate the further development and application of DT technology in precision oncology.

Supplementary Information

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Supplementary material 1

Supplementary material 2

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Author contributions
SS conceptualized the study, set the research methodology, performed data visualization, and edited the manuscript. WQ conceptualized the study and revised the manuscript. XL, JZ, GLand SL organized the data and set the research methodology. SC conceptualized the study, reviewed and edited the manuscript, acquired funding, managed the project, and performed formal analysis. XZ, BW, JY, YS, BW, LJ and CD conducted formal analysis and supervision.

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Availability of data and materials
The data sets generated and analyzed during this study are available from the corresponding author on reasonal request.

Declarations

Ethics approval and consent to participate
Since this study is a retrospective analysis of existing published research, ethical committee approval is not required.

Consent for publication
Not appliable.

Competing interests
The authors declare that they have no competing interests.

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References

1. **Cancer**. https://www.who.int/news-room/fact-sheets/detail/cancer.
2. Dentro SC, Leshchiner I, Haase K, Tarabichi M, Wintersinger J, Deshwar AG, Yu KX, Rubanova Y, Macintyre G, Demeulemeester J, et al. Characterizing genetic intra-tumor heterogeneity across 2658 human cancer genomes. Cell. 2021;184(8):2239.
3. Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. Nature. 2013;501(7467):338–45.
4. Sainz-DeMena D, García-Aznar JM, Pérez MA, Borau C. Im2mesh: a python library to reconstruct 3D meshes from scattered data and 2D segmentations, application to patient-specific neuroblastoma tumour image sequences. Appl Sci-Basel. 2022;12(22):15.
5. Rabbie R, Lau D, White RM, Adams DJ. Unraveling the cartography of the cancer ecosystem. Genome Biol. 2021;22(1):9.
6. Merlo LMF, Pepper JW, Reid BJ, Maley CC. Cancer as an evolutionary and ecological process. Nat Rev Cancer. 2006;6(12):924–35.
7. Wang JJ, Lei KF, Han F. Tumor microenvironment: recent advances in various cancer treatments. Eur Rev Med Pharmacol Sci. 2018;22(12):3855–64.
8. Harbeck N, Wuerstlein R. Truly personalized therapy - an end to the era of one size fits all. Nat Rev Clin Oncol. 2019;16(2):77–8.
9. Hernandez-Boussard T, Macklin P, Greenspan EJ, Gryshuk AL, Stahlberg E, Syeda-Mahmood T, Shmulevich I. Digital twins for predictive oncology will be a paradigm shift for precision cancer care. Nat Med. 2021;27(12):2065–6.
10. Rasheed A, San O, Kvamsdal T. digital twin: values, challenges and enablers from a modeling perspective. IEEE Access. 2020;8:21980–2012.

11. Kapteyn MG, Pretorius JVR, Willcox KE. A probabilistic graphical model foundation for enabling predictive digital twins at scale. Nat Comput Sci. 2021;1(5):337.
12. Laubenbacher R, Sluka JP, Glazier JA. Using digital twins in viral infection. Science. 2021;371(6534):1105–6.
13. Niederer SA, Sacks MS, Girolami M, Willcox K. Scaling digital twins from the artisanal to the industrial. Nat Comput Sci. 2021;1(5):313–20.
14. Wu CY, Lorenzo G, Hormuth DA II, Lima E, Slavkova KP, DiCarlo JC, Virostko J, Phillips CM, Patt D, Chung C, et al. Integrating mechanism-based modeling with biomedical imaging to build practical digital twins for clinical oncology. Biophys Rev. 2022;3(2):23.
15. National Academy of E, National Academies of Sciences E, Medicine: Foundational Research Gaps and Future Directions for Digital Twins. The National Academies Press. 2024.
16. Metzcar J, Jutzeler CR, Macklin P, Köhn-Luque A, Brüningk SC. A review of mechanistic learning in mathematical oncology. Front Immunol. 2024;15:1363144.
17. Laubenbacher R, Mehrad B, Shmulevich I, Trayanova N. Digital twins in medicine. Nat Comput Sci. 2024;4(3):184–91.
18. Rivera LF, Jiménez M, Angara P, Villegas NM, Tamura G, Müller HA: Towards continuous monitoring in personalized healthcare through digital twins. In: Proceedings of the 29th annual international conference on computer science and software engineering: 2019; 2019: 329–335.
19. Wu C, Lorenzo G, Hormuth DA 2nd, Lima E, Slavkova KP, DiCarlo JC, Virostko J, Phillips CM, Patt D, Chung C, et al. Integrating mechanism-based modeling with biomedical imaging to build practical digital twins for clinical oncology. Biophys Rev. 2022;3(2): 021304.
20. Gilbertson RJ, Behjati S, Böttcher AL, Bronner ME, Burridge M, Clausing H, Clifford H, Danaher T, Donovan LK, Drost J, et al. The virtual child. Cancer Discov. 2024;14(4):663–8.
21. Wickramasinghe N, Jayaraman PP, Forkan ARM, Ulapane N, Kaul R, Vaughan S, Zelcer J. A vision for leveraging the concept of digital twins to support the provision of personalized cancer care. IEEE Int Comput. 2022;26(5):17–24.
22. Stahlberg EA, Abdel-Rahman M, Aguilar B, Asadpoure A, Beckman RA, Borkon LL, Bryan JN, Cebulla CM, Chang YH, Chatterjee A, et al. Exploring approaches for predictive cancer patient digital twins: opportunities for collaboration and innovation. Front Digit Health. 2022;4:1007784.
23. Wu CY, Jarrett AM, Zhou ZJ, Elshafeey N, Adrada BE, Candelaria RP, Mohamed RMM, Boge M, Huo L, White JB, et al. MRI-based digital models forecast patient-specific treatment responses to neoadjuvant chemotherapy in triple-negative breast cancer. Cancer Res. 2022;82(18):3394–404.
24. Kim JK, Lee SJ, Hong SH, Choi IY. Machine-learning-based digital twin system for predicting the progression of prostate cancer. Appl Sci-Basel. 2022;12(16):12.
25. Cobo MJ, López-Herrera AG, Herrera-Viedma E, Herrera F. Science mapping software tools: review, analysis, and cooperative study among tools. J Am Soc Inf Sci Technol. 2011;62(7):1382–402.
26. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Annals of Internal Medicine 2018. 169(7):467–473.
27. Aijing LSY, Lu M. Medical literature information retrieval. Third Edition edn: People's Medical Publishing House; 2005.
28. Group F-NBW. In: BEST (Biomarkers, EndpointS, and other Tools) Resource. edn. Silver Spring (MD) Bethesda (MD): Food and Drug Administration (US) National Institutes of Health (US); 2016.
29. Friedman LMF, DeMets DL. Fundamentals of clinical trials. New York: Springer; 2010.
30. Sozu T, Sugimoto T, Hamasaki T, Evans SR. Sample size determination in clinical trials with multiple endpoints. Cham: Springer International Publishing AG; 2015.
31. Lu Y, Liu C, Wang KIK, Huang H, Xu X. Digital twin-driven smart manufacturing: connotation, reference model, applications and research issues. Robot Computer Integr Manufact. 2020. https://doi.org/10.1016/j.rcim.2019.101837.
32. Grieves M, Vickers, J. 2017. Digital Twin: Mitigating Unpredictable, Undesirable Emergent Behavior in Complex Systems. In: Transdisciplinary Perspectives on Complex Systems edn. Edited by Kahlen JF, S., Alves, A. Cham Springer; 2017: 85–113.
33. Osinska V, Klimas R. Mapping science: tools for bibliometric and altmetric studies. Inform Res Int Electron J. 2021;26:10.
34. Qi W, Zhu X, He D, Wang B, Cao S, Dong C, Li Y, Chen Y, Wang B, Shi Y, et al. Mapping knowledge landscapes and emerging trends in AI for dementia biomarkers: bibliometric and visualization analysis. J Med Int Res. 2024;26: e57830.
35. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2009;84(2):523–38.
36. He D, Cao S, Le Y, Wang M, Chen Y, Qian B. Virtual reality technology in cognitive rehabilitation application: bibliometric analysis. JMIR Serious Games. 2022;10(4): e38315.
37. Zhang J, Li L, Lin GJ, Fang D, Tai YH, Huang JC. Cyber resilience in healthcare digital twin on lung cancer. IEEE Access. 2020;8:201900–13.
38. Béthencourt L, Dabachine W, Dejouy V, Lalmiche Z, Neuberger K, Ibnouhsein I, Chéreau S, Mathelin C, Savy N, Pierre PS, et al. Guiding measurement protocols of connected medical devices using digital twins: a statistical methodology applied to detecting and monitoring lymphedema. IEEE Access. 2021;9:39444–65.
39. Wang Y, Thaker K, Hui V, Brusilovsky P, He D, Donovan H, Lee YJ. Utilizing digital twin to create personas representing ovarian cancer patients and their families. Stud Health Technol Inform. 2024;315:754–6.
40. Obergfell T, Nydegger KN, Heesen P, Schelling G, Bode-Lesniewska B, Studer G, Fuchs B. SwissSarcomaNetwork: improving sarcoma outcomes: target trial emulation to compare the impact of unplanned and planned resections on the outcome. Cancers. 2024;16(13):15.
41. Cukic M, Annaheim S, Bahrami F, Defraeye T, De Nys K, Jörger M. Is personal physiology-based rapid prediction digital twin for minimal effective fentanyl dose better than standard practice: a pilot study protocol. BMJ Open. 2024;14(9):11.
42. Servin F, Collins JA, Heiselman JS, Frederick-Dyer KC, Planz VB, Geevarghese SK, Brown DB, Jarnagin WR, Miga MI. Simulation of image-guided microwave ablation therapy using a digital twin computational model. IEEE Open J Eng Med Biol. 2024;5:107–24.
43. Checcucci E, Amparore D, Volpi G, De Cillis S, Piramide F, Verri P, Piana A, Sica M, Gatti C, Alessio P, et al. Metaverse surgical planning with three-dimensional virtual models for minimally invasive partial nephrectomy. Eur Urol. 2024;85(4):320–5.
44. Jeising S, Liu S, Blaszczyk T, Rapp M, Beez T, Cornelius JF, Schwerter M, Sabel M. Combined use of 3D printing and mixed reality technology for neurosurgical training: getting ready for brain surgery. Neurosurg Focus. 2024;56(1):12.
45. Shi YY, Deng XS, Tong YQ, Li RT, Zhang YF, Ren LJ, Si WX. Synergistic digital twin and holographic augmented-reality-guided percutaneous puncture of respiratory liver tumor. IEEE T Hum-Mach Syst. 2022;52(6):1364–74.
46. Su P, Yue C, Cui L, Zhang Q, Liu B, Liu T. Quasi-static mechanical properties and continuum constitutive model of the thyroid gland. J Functional Biomater. 2022;13(4):283.
47. Konöopik J, Wolf L, Schffski O. Digital twins for breast cancer treatment - an empirical study on stakeholders' perspectives on potentials and challenges. Health Technol. 2023;13(6):1003–10.
48. Joslyn LR, Huang W, Miles D, Hosseini I, Ramanujan S. Digital twins elucidate critical role of T(scm) in clinical persistence of TCR-engineered cell therapy. NPJ Syst Biol Appl. 2024;10(1):11.
49. Shi H, Li J, Guo L, Mei X. Control performance evaluation of serial urology manipulator by virtual prototyping. Chin J Mechan Eng. 2021. https://doi.org/10.1186/s10033-021-00534-x.
50. Monji-Azad S, Männle D, Hesser J, Pohlmann J, Rotter N, Affolter A, Weis CA, Ludwig S, Scherl C. Point cloud registration for measuring shape dependence of soft tissue deformation by digital twins in head and neck surgery. Biomed Hub. 2024;9(1):9–15.
51. Xu Q, Kowalski J. myCMIE: My cancer molecular information exchange. iScience. 2023;26(8):107324.
52. Chang HC, Gitau AM, Kothapalli S, Welch DR, Sardiu ME, McCoy MD. Understanding the need for digital twins' data in patient advocacy and forecasting oncology. Front Artif Intell. 2023;6:5.
53. Reimann AM, Schalk E, Jost F, Mougiakakos D, Weber D, Döhner H, Récher C, Dumas PY, Ditzhaus M, Fischer T, et al. AML consolidation therapy: timing matters. J Cancer Res Clin Oncol. 2023;149(15):13811–21.

54. Moztarzadeh O, Jamshidi M, Sargolzaei S, Jamshidi A, Baghalipour N, Moghani MM, Hauer L. Metaverse and healthcare: machine learning-enabled digital twins of cancer. Bioeng Basel. 2023;10(4):23.
55. Gonzalez-Abril L, Angulo C, Ortega JA, Lopez-Guerra JL. Generative adversarial networks for anonymized healthcare of lung cancer patients. Electronics. 2021;10(18):17.
56. Islam MN, Hasan M, Hossain MK, Alam MGR, Uddin MZ, Soylu A. Vision transformer and explainable transfer learning models for auto detection of kidney cyst, stone and tumor from CT-radiography. Sci Rep. 2022;12(1):14.
57. Batch KE, Yue JW, Darcovich A, Lupton K, Liu CC, Woodlock DP, El Amine MAK, Causa-Andrieu PI, Gazit L, Nguyen GH, et al. Developing a cancer digital twin: supervised metastases detection from consecutive structured radiology reports. Front Artif Intell. 2022;5:10.
58. Ganaie MA, Tanveer M. Alzheimers Dis Neuroimaging I: KNN weighted reduced universum twin SVM for class imbalance learning. Knowledge-Based Syst. 2022;245:15.
59. Wang TJ, Dremel J, Richter S, Polanski W, Uckermann O, Eyüpoglu I, Czarske JW, Kuschmierz R. Resolution-enhanced multi-core fiber imaging learned on a digital twin for cancer diagnosis. Neurophotonics. 2024;11:7.
60. Fuchs B, Schelling G, Elyes M, Studer G, Bode-Lesniewska B, Scaglioni MF, Giovanoli P, Heesen P, Wong DV. Unlocking the power of benchmarking: real-world-time data analysis for enhanced sarcoma patient outcomes. Cancers. 2023;15(17):17.
61. Bahrami F, Rossi RM, De Nys K, Defraeye T. An individualized digital twin of a patient for transdermal fentanyl therapy for chronic pain management. Drug Deliv Transl Res. 2023;13(9):2272–85.
62. Chang HC, Gitau AM, Kothapalli S, Welch DR, Sardiu ME, McCoy MD. Understanding the need for digital twins' data in patient advocacy and forecasting oncology. Front Artif Intell. 2023;6:1260361.
63. Rukhlenko OS, Imoto H, Tambde A, McGillycuddy A, Junk P, Tuliakova A, Kolch W, Kholodenko BN. Cell state transition models stratify breast cancer cell phenotypes and reveal new therapeutic targets. Cancers. 2024;16(13):210.
64. Moztarzadeh O, Jamshidi M, Sargolzaei S, Jamshidi A, Baghalipour N, Moghani MM, Hauer L. Metaverse and healthcare: machine learning-enabled digital twins of cancer. Bioeng Basel. 2023;10(4):210.
65. Tardini E, Zhang XH, Canahuate G, Wentzel A, Mohamed ASR, Van Dijk L, Fuller CD, Marai GE. Optimal Treatment selection in sequential systemic and locoregional therapy of oropharyngeal squamous carcinomas: deep Q-learning with a patient-physician digital twin Dyad. J Med Int Res. 2022;24(4):21.
66. Keller J, Lindenmeyer A, Blattmann M, Gaebel J, Schneider D, Neumuth T, Franke S. Using digital twins to support multiple stages of the patient journey. Stud Health Technol Inform. 2023;301:227–32.
67. Tel A, Zeppieri M, Robiony M, Sembronio S, Vinayahalingam S, Pontoriero A, Pergolizzi S, Angileri FF, Spadea L, Ius T. Exploring deep cervical compartments in head and neck surgical oncology through augmented reality vision: a proof of concept. J Clin Med. 2023;12(20):6650.
68. Wentzel A, Attia S, Zhang X, Canahuate G, Fuller CD, Marai GE. DITTO: A visual digital twin for interventions and temporal treatment outcomes in head and neck cancer. IEEE Trans Vis Comput Graph. 2024. https://doi.org/10.1109/TVCG.2024.3456160.
69. Hu MD, Zhong Y, Xie SX, Lv HB, Lv ZH. Fuzzy System based medical image processing for brain disease prediction. Front Neurosci. 2021;15:13.
70. Sarris AL, Sidiropoulos E, Paraskevopoulos E, Bamidis P. Towards a digital twin in human brain: brain tumor detection using K-means. Stud Health Technol Inform. 2023;302:1052–6.
71. Jeising S, Liu S, Blaszczyk T, Rapp M, Beez T, Cornelius JF, Schwerter M, Sabel M. Combined use of 3D printing and mixed reality technology for neurosurgical training: getting ready for brain surgery. Neurosurg Focus. 2024;56(1):E12.
72. Gonzalez-Abril L, Angulo C, Ortega JA, Lopez-Guerra JL. Statistical validation of synthetic data for lung cancer patients generated by using generative adversarial networks. Electronics. 2022;11(20):15.
73. Tai Y, Zhang L, Li Q, Zhu C, Chang V, Rodrigues JJPC, Guizani M. Digital-twin-enabled IoMT system for surgical simulation using rAC-GAN. IEEE Int Things J. 2022;9(21):20918–31.
74. Chaudhuri A, Pash G, Hormuth DA II, Lorenzo G, Kapteyn M, Wu CY, Lima E, Yankeelov TE, Willcox K. Predictive digital twin for optimizing patient-specific radiotherapy regimens under uncertainty in high-grade gliomas. Front Artif Intell. 2023;6:20.
75. Christenson C, Wu CY, Ii DAH, Stowers CE, Lamonica M, Ma JF, Rauch GM, Yankeelov TE. Fast model calibration for predicting the response of breast cancer to chemotherapy using proper orthogonal decomposition. J Comput Sci. 2024;82:14.
76. Moore JH, Li X, Chang JH, Tatonetti NP, Theodorescu D, Chen Y, Asselbergs FW, Venkatesan M, Wang ZP. SynTwin: a graph-based approach for predicting clinical outcomes using digital twins derived from synthetic patients. Pac Symp Biocomput. 2024;29:96–107.
77. Susilo ME, Li CC, Gadkar K, Hernandez G, Huw LY, Jin JY, Yin S, Wei MC, Ramanujan S, Hosseini I. Systems-based digital twins to help characterize clinical dose-response and propose predictive biomarkers in a Phase I study of bispecific antibody, mosunetuzumab. NHL CTS-Clin Transl Sci. 2023;16(7):1134–48.
78. Lukaniszyn M, Majka L, Grochowicz B, Mikolajewski D, Kawala-Sterniuk A. Digital twins generated by artificial intelligence in personalized healthcare. Appl Sci-Basel. 2024;14(20):17.
79. Mösch A, Grazioli F, Machart P, Malone B. NeoAgDT: optimization of personal neoantigen vaccine composition by digital twin simulation of a cancer cell population. Bioinformatics. 2024;40(5):10.
80. Arulraj T, Wang H, Ippolito A, Zhang S, Fertig EJ, Popel AS. Leveraging multi-omics data to empower quantitative systems pharmacology in immuno-oncology. Brief Bioinform. 2024. https://doi.org/10.1093/bioinformatics/btae205.
81. Baumgartner C. The world's first digital cell twin in cancer electrophysiology: a digital revolution in cancer research? J Exp Clin Cancer Res. 2022;41(1):298.
82. Arulraj T, Wang HW, Ippolito A, Zhang SM, Fertig EJ, Popel AS. Leveraging multi-omics data to empower quantitative systems pharmacology in immuno-oncology. Brief Bioinform. 2024;25(3):4.
83. Kolokotroni E, Abler D, Ghosh A, Tzamali E, Grogan J, Georgiadi E, Büchler P, Radhakrishnan R, Byrne H, Sakkalis V, et al. A multidisciplinary hyper-modeling scheme in personalized in silico oncology: coupling cell kinetics with metabolism, signaling networks, and biomechanics as plug-in component models of a cancer digital twin. J Pers Med. 2024;14(5):37.
84. Wang HW, Arulraj T, Ippolito A, Popel AS. From virtual patients to digital twins in immuno-oncology: lessons learned from mechanistic quantitative systems pharmacology modeling. Npj Digit Med. 2024;7(1):6.
85. Shmatko A, Ghaffari Laleh N, Gerstung M, Kather JN. Artificial intelligence in histopathology: enhancing cancer research and clinical oncology. Nat Cancer. 2022;3(9):1026–38.
86. Ahmadian H, Mageswaran P, Walter BA, Blakaj DM, Bourekas EC, Mendel E, Marras WS, Soghrati S. A digital twin for simulating the vertebroplasty procedure and its impact on mechanical stability of vertebra in cancer patients. Int J Numer Methods Biomed Eng. 2022. https://doi.org/10.1002/cnm.3600.
87. Ahmadian H, Mageswaran P, Walter BA, Blakaj DM, Bourekas EC, Mendel E, Marras WS, Soghrati S. Toward an artificial intelligence-assisted framework for reconstructing the digital twin of vertebra and predicting its fracture response. Int J Numer Method Biomed Eng. 2022;38(6): e3601.
88. Singh Y, Hathaway QA, Erickson BJ. Generative AI in oncological imaging: revolutionizing cancer detection and diagnosis. Oncotarget. 2024;15:607–8.
89. Sharma V, Kumar A, Sharma K. Digital twin application in women's health: cervical cancer diagnosis with CervixNet. Cogn Syst Res. 2024;87:12.
90. Wan ZB, Dong YQ, Yu ZC, Lv HB, Lv ZH. Semi-supervised support vector machine for digital twins based brain image fusion. Front Neurosci. 2021;15:12.
91. Bretti G, De Ninno A, Natalini R, Peri D, Roselli N. Estimation algorithm for a hybrid PDE-ODE model inspired by immunocompetent cancer-on-chip experiment. Axioms. 2021;10(4):243.
92. Bomberna T, Maleux G, Debbaut C. Simplification strategies for a patient-specific CFD model of particle transport during liver radioembolization. Comput Biol Med. 2024;178: 108732.

93. Shishlenin M, Kozelkov A, Novikov N. Nonlinear medical ultrasound tomography: 3D modeling of sound wave propagation in human tissues. Mathematics. 2024;12(2):14.
94. Grieb N, Schmierer L, Kim HU, Strobel S, Schulz C, Meschke T, Kubasch AS, Brioli A, Platzbecker U, Neumuth T, et al. A digital twin model for evidence-based clinical decision support in multiple myeloma treatment. Front Digit Health. 2023;5:14.
95. Sasikaladevi N, Revathi A. Digital twin of renal system with CT-radiography for the early diagnosis of chronic kidney diseases. Biomed Signal Process Control. 2024;88:10.
96. Bahrami F, Rossi RM, De Nys K, Joerger M, Radenkovic MC, Defraeye T. Implementing physics-based digital patient twins to tailor the switch of oral morphine to transdermal fentanyl patches based on patient physiology. Eur J Pharm Sci. 2024;195:19.
97. Bahrami F, Psikuta A, Dommann A, Defraeye T. Exploring the thermally-controlled fentanyl transdermal therapy to provide constant drug delivery by physics-based digital twins. Eur J Pharm Sci. 2024;200:14.
98. Fuchs B, Schelling G, Elyes M, Studer G, Bode-Lesniewska B, Scaglioni MF, Giovanoli P, Heesen P. Unlocking the power of benchmarking: real-world-time data analysis for enhanced sarcoma patient outcomes. Cancers. 2023;15(17):4395.
99. Eftekhar Z, Aghaei M, Saki N. DNA damage repair in megakaryopoiesis: molecular and clinical aspects. Expert Rev Hematol. 2024;17(10):705–12.
100. Tene T, Vique López DF, Valverde Aguirre PE, Orna Puente LM, Vacacela Gomez C. Virtual reality and augmented reality in medical education: an umbrella review. Front Digit Health. 2024;6:1365345.
101. Zohdi TI, Zohdi-Mofid M. Rapid machine-learning enabled design and control of precise next-generation cryogenic surgery in dermatology. Computer Methods Appl Mechan Eng. 2023;12:417.
102. Urcun S, Rohan P-Y, Skalli W, Nassoy P, Bordas SPA, Sciume G. Digital twinning of cellular capsule technology: emerging outcomes from the perspective of porous media mechanics. PLos One. 2021;16(7):210.
103. Migliaccio G, Ferraro R, Wang ZH, Cristini V, Dogra P, Caserta S. Exploring cell migration mechanisms in cancer: from wound healing assays to cellular automata models. Cancers. 2023;15(21):14.
104. Valentim CA, Rabi JA, David SA. Cellular-automaton model for tumor growth dynamics: virtualization of different scenarios. Comput Biol Med. 2023;153: 106481.
105. Merchant N, Sampson AT, Boiko A, Falconer RE. Dense agent-based HPC simulation of cell physics and signaling with real-time user interactions. Front Comput Sci-Switz. 2023;5:26.
106. Rukhlenko OS, Imoto H, Tambde A, McGillycuddy A, Junk P, Tuliakova A, Kolch W, Kholodenko BN. Cell state transition models stratify breast cancer cell phenotypes and reveal new therapeutic targets. Cancers. 2024;16(13):25.
107. Joslyn LR, Huang W, Miles D, Hosseini I, Ramanujan S. Digital twins elucidate critical role of T(scm) in clinical persistence of TCR-engineered cell therapy. Npj Syst Biol Appl. 2024. https://doi.org/10.1038/s41540-024-00335-7.
108. Rajabi L, Ebrahimdoost M, Mohammadi SA, Soleimani Samarkhazan H, Khamisipour G, Aghaei M. Aqueous and ethanolic extracts of Moringa oleifera leaves induce selective cytotoxicity in Raji and Jurkat cell lines by activating the P21 pathway independent of P53. Mol Biol Rep. 2025;52(1):102.
109. Li G, Chen YB, Peachey J. Construction of a digital twin of chronic graft vs host disease patients with standard of care. Bone Marrow Trans. 2024;59(9):1280–5.
110. Salimi Y, Hajianfar G, Mansouri Z, Sanaat A, Amini M, Shiri I, Zaidi H. Organomics a concept reflecting the importance of PET/CT healthy organ radiomics in non-small cell lung cancer prognosis prediction using machine learning. Clin Nucl Med. 2024;49(10):899–908.
111. Qi T, Cao Y. Virtual clinical trials: a tool for predicting patients who may benefit from treatment beyond progression with pembrolizumab in non-small cell lung cancer. CPT Pharmacometrics Syst Pharmacol. 2023;12(2):236–49.
112. EDITH: European Virtual Human Twin. https://www.edith-csa.eu/.
113. SDTC—Swedish Digital Twin Consortium. https://www.sdtc.se/#consortium.
114. NSF, NIH and FDA support research in digital twin technology for biomedical applications. https://new.nsf.gov/news/nsf-nih-fda-support-research-digital-twin-technology.
115. Geuna A. The changing rationale for european university research funding: are there negative unintended consequences? J Econ Issues. 2001;35(3):607–32.
116. Tao F, Qi Q. Make more digital twins. Nature. 2019;573(7775):490–1.
117. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science. 2013;339(6127):1546–58.
118. Łukaniszyn M, Majka Ł, Grochowicz B, Mikołajewski D, Kawala-Sterniuk A. Digital twins generated by artificial intelligence in personalized healthcare. Appl Sci. 2024;14(20):9404.
119. Aldridge S, Teichmann SA. Single cell transcriptomics comes of age. Nat Commun. 2020;11(1):4307.
120. Katsoulakis E, Wang Q, Wu H, Shahriyari L, Fletcher R, Liu J, Achenie L, Liu H, Jackson P, Xiao Y, et al. Digital twins for health: a scoping review. NPJ Digit Med. 2024;7(1):77.
121. Fuchs B, Studer G, Bode-Lesniewska B, Heesen P. The next frontier in sarcoma care: digital health, AI, and the quest for precision medicine. J Pers Med. 2023;13(11):1530.
122. Xu D, Ouyang Z, Dong Y, Yu H-Y, Zheng S, Li S, Tam KC. Robust, breathable and flexible smart textiles as multifunctional sensor and heater for personal health management. Adv Fiber Mater. 2023;5(1):282–95.
123. Rankin D, Black M, Bond R, Wallace J, Mulvenna M, Epelde G. Reliability of supervised machine learning using synthetic data in health care: model to preserve privacy for data sharing. JMIR Med Inform. 2020;8(7):e18910.
124. Potter D, Brothers R, Kolacevski A, Koskimaki JE, McNutt A, Miller RS, Nagda J, Nair A, Rubinstein WS, Stewart AK, et al. Development of CancerLinQ, a health information learning platform from multiple electronic health record systems to support improved quality of care. JCO Clin Cancer Inform. 2020;4:929–37.
125. Mzili T, Mzili I, Riffi M, Pamucar D, Simic V, Abualigah L. Hybrid genetic and penguin search optimization algorithm (GA-PSEOA) for efficient flow shop scheduling solutions. Facta Univ Series Mechan Eng. 2023;22:10.
126. Katsoulakis E, Wang Q, Wu HM, Shahriyari L, Fletcher R, Liu JW, Achenie L, Liu HF, Jackson P, Xiao Y, et al. Digital twins for health: a scoping review. npj Digit Med. 2024;7(1):11.
127. Kemkar S, Tao MD, Ghosh A, Stamatakos G, Graf N, Poorey K, Balakrishnan U, Trask N, Radhakrishnan R. Towards verifiable cancer digital twins: tissue level modeling protocol for precision medicine. Front Physiol. 2024;15:15.
128. DigiTwins Consortium. [http://www.digitwins.org/consortium]
129. Digital Twin Consortium. https://www.digitaltwinconsortium.org/index.html
130. Li SM, Zhou BS. A review of radiomics and genomics applications in cancers: the way towards precision medicine. Radiat Oncol. 2022;17(1):10.
131. Jeremiah SR, El Azzaoui A, Xiong NN, Park JH. A comprehensive survey of digital twins: applications, technologies and security challenges. J Syst Architect. 2024;151:21.
132. Zouache DA, Boumaza L. A guided epsilon-dominance arithmetic optimization algorithm for effective multi-objective optimization in engineering design problems. Multimed Tools Appl. 2024;83:31673–700.
133. Yin XF, Zhu YM, Hu JK. A comprehensive survey of privacy-preserving federated learning: a taxonomy, review, and future directions. ACM Comput Surv. 2021;54(6):36.
134. Linli Li F, Li H, Guo J, Xinjian G. Digital twin bionics: a biological evolution-based digital twin approach for rapid product development. IEEE Access. 2021;2021(9):121507–21.
135. Wang MB, Hu HJ, Wu S. Opportunities and challenges of digital twin technology in healthcare. Chin Med J. 2023;136(23):2895–6.
136. Balasubramanyam A, Ramesh R, Sudheer R, Honnavalli PB. Revolutionizing healthcare: a review unveiling the transformative power of digital twins. IEEE Access. 2024;12:69652–76.
137. Got A, Zouache D, Moussaoui A, Abualigah L, Alsayat A. Improved manta ray foraging optimizer-based SVM for feature selection problems: a medical case study. J Bionic Eng. 2024;21(1):409–25.
138. Lorenzo G, Ahmed SR, Hormuth DA, Vaughn B, Kalpathy-Cramer J, Solorio L, Yankeelov TE, Gomez H. Patient-specific, mechanistic models

of tumor growth incorporating artificial intelligence and big data. Annu Rev Biomed Eng. 2024;26:529–60.
139. Zouache DG, Alarabiat A, et al. A novel multi-objective wrapper-based feature selection method using quantum-inspired and swarm intelligence techniques. Multimed Tools Appl. 2024;83:22811–35.
140. Ahmad MAT, A.; Eckert, C. 2018. Interpretable machine learning in healthcare. In: IEEE International Conference on Healthcare Informatics (ICHI). New York, NY, USA: IEEE; 2018: 447–447.
141. Kaur HN, Harsha; Jenkins, Samuel; Caruana, Rich; Wallach, Hanna; Wortman Vaughan, Jennifer: Interpreting Interpretability: Understanding Data Scientists' Use of Interpretability Tools for Machine Learning. In: Proceedings of the 2020 CHI Conference on Human Factors in Computing Systems (CHI '20). New York, NY, USA: Association for Computing Machinery; 2020: 1–14.
142. Saki N, Haybar H, Aghaei M. Subject: motivation can be suppressed, but scientific ability cannot and should not be ignored. J Transl Med. 2023;21(1):520.
143. Aghaei M, Khademi R, Bahreiny SS, Saki N. The need to establish and recognize the field of clinical laboratory science (CLS) as an essential field in advancing clinical goals. Health Sci Rep. 2024;7(8): e70008.
144. G Li 2024. A new regulatory road in clinical trials: Digital Twins. 10 12

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