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REVIEW

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Recent advances in 3D printing applications for CNS tumours

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Abstract

Three-dimensional printing (3DP) has emerged as a transformative technology in the field of central nervous system (CNS) tumours, offering innovative advancements in various aspects of diagnosis, treatment and education. By precisely replicating the microenvironment of CNS tumours, modelling tumour vascularisation, and capturing genetic heterogeneity, 3DP enables the development of targeted therapies and personalised treatment strategies. The technology has markedly enhanced preoperative planning and intraoperative guidance, providing highly accurate, patient-specific models that improve tumour localisation, facilitate tailored surgical planning, and offer superior visualisation of complex anatomical structures. Furthermore, 3DP has revolutionised education and training for neurosurgeons, trainees, and patients by delivering realistic simulations that enhance surgical skills and decision-making. Despite its transformative potential, the widespread adoption of 3DP faces challenges, including material biocompatibility issues, high costs, and technical limitations. Furthermore, the ethical and regulatory landscape for 3DP in clinical practice requires further development. This review concludes that while 3DP offers significant promise for advancing CNS tumour treatment, ongoing research is essential to address these challenges and optimising its clinical impact.

Keywords Three dimensional printing, CNS tumours, Neuro oncology, Neurosurgery

Introduction

Central nervous system (CNS) tumours, which develop in the brain, spinal cord, or surrounding structures, are some of the most complex and challenging cancers to treat. Although these tumours account for only 1.6% of all cancers, they disproportionately affect patients and are the leading cause of cancer-related mortality in children and adolescents [1]. The World Health Organization classifies CNS tumours into more than 100 different types, each with a unique molecular profile and clinical behaviour. Among these, high-grade gliomas, particularly glioblastomas, are particularly aggressive. Despite intensive treatment strategies, median survival for glioblastoma patients is often limited to a few months [2].

Standard treatment for CNS tumours typically involves a combination of maximal surgical resection, radiotherapy, and chemotherapy. Each of these

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modalities has significant challenges. Surgical resection is critical for reducing tumour size and obtaining diagnostic information, but is often limited by the infiltrative nature of the tumour and its proximity to critical brain areas, which increases the risk of neurological damage [3]. Radiotherapy can help control tumour regrowth, but can lead to neurotoxicity, particularly when tumours are close to sensitive brain regions [2]. Chemotherapy faces its own hurdles, such as the blood–brain barrier, which limits drug delivery, and the inherent resistance of tumour cells to many treatments [4].

In light of these challenges, neuro-oncology is increasingly exploring innovative and personalised treatment approaches. Advances in molecular genetics have paved the way for targeted therapies that focus on specific genetic and epigenetic alterations in tumour cells [5]. Improvements in imaging technologies, including intraoperative magnetic resonance imaging (MRI) and advanced functional imaging, are increasing the precision of surgical and radiotherapeutic procedures [6]. Despite these advances, effective treatment remains elusive, highlighting the need for novel technologies to further improve patient outcomes.

One such emerging technology is three-dimensional printing (3DP), or additive manufacturing (AM). This technology has the potential to transform neuro-oncology by providing precise, patient-specific anatomical models that enhance pre-operative planning. Surgeons can use these models to better visualise and simulate complex procedures, potentially reducing intraoperative risks and improving surgical outcomes [7]. In addition, 3DP implants and scaffolds are being developed to improve outcomes in reconstructive neurosurgery, offering better tissue integration and fewer postoperative complications [7]. The future of 3DP also holds promise in the field of bioprinting, where living cells are printed to create tissue-like structures for personalised drug testing and neural tissue regeneration [8]. However, the integration of 3DP into neuro-oncology is not without its challenges. The need for high-resolution, biocompatible materials, coupled with the evolving regulatory landscape, poses significant hurdles. In addition, the high cost and limited availability of this technology may hinder its wider adoption, particularly in resource-limited settings [9].

This review aims to critically evaluate the role of 3DP in managing CNS tumours, focusing on its potential to improve surgical precision, enhance therapeutic approaches, and ultimately contribute to better patient outcomes and quality of life.

Methodology

This review aims to provide a comprehensive overview of the various applications of 3DP in CNS tumours. A thorough literature search was conducted in several databases, including PubMed/MEDLINE, EMBASE, Cochrane Library and SCOPUS, using the keywords "3D printing," "bioprinting, " "brain tumours, " "CNS tumours, " "glioblastoma, " "neurosurgery, " "additive manufacturing, " "patient-specific implants, " "3D-printed tumour models," "biomaterials in neuro-oncology," "3D-printed scaffolds," "tumour microenvironment," "personalised medicine in neurosurgery," "preoperative surgical planning," "3D-printed chemotherapy implants," "drug delivery systems in CNS tumours," "neurosurgical simulation models," and "customised cranioplasty" were used in combination with additional terms including "tumour modelling," "brain tumour reconstruction," "biofabrication for CNS tumours," "precision oncology with 3D printing," "polymer-based 3D scaffolds," "nanoparticle integration in 3D printing," "MRI-based 3D printing for neurosurgery," and "hydrogel-based 3D scaffolds.". In addition to the comprehensive database search, references cited in recent reviews focused on similar topics were manually examined to identify additional sources that could contribute to the search strategy. The search was guided by pre-defined inclusion criteria and focused only on articles published in English. Strict exclusion criteria were applied to ensure scientific rigour, eliminating stand-alone abstracts, posters, case reports and non-peer-reviewed articles, while prioritising high quality, peer-reviewed studies. In order to ensure a broad representation of the literature, no limit was placed on the number of studies. This allowed a comprehensive inclusion of descriptive, observational, cohort and animal model experimental studies. A summary of the methodology is provided in Table 1.

Overview of 3DP

History and evolution

3DP, also known as AM, is a transformative process that converts digital designs into physical objects by sequentially adding material layer by layer [10]. Since its inception in the early nineteenth century, 3DP has undergone significant evolution. A pivotal moment in this evolution occurred on 9 March 1983, when American scientist Charles W. "Chuck" Hull developed the first 3D printer using a stereolithography apparatus (SLA-1) to produce a teacup [10, 11]. Hull's invention marked the advent of modern AM technology and set the stage for subsequent innovations.

Following Hull's groundbreaking work, numerous advancements have further refined 3DP technologies.

Table 1 Summary of methodology

Methodology steps	Description
Literature search	PubMed/MEDLINE, EMBASE, Scopus and the Cochrane Library
Inclusion criteria	Original studies including randomised controlled trials, prospective and retrospective cohort studies, case–control studies, and case series. Studies involving either paediatric and/or adult patients with CNS tumours where 3D printing was applied in surgical planning, tumour modelling, patient-specific implants, or drug delivery systems. Articles written in English
Exclusion criteria	Non-English studies. Stand-alone abstracts, conference posters, unpublished studies, and non-peer-reviewed papers. Studies without direct application of 3D printing to CNS tumours or those with sample sizes of fewer than five patients in clinical settings or insufficient reproducibility in experimental studies
Search terms	Key words such as "3D printing,""bioprinting,""brain tumours,""CNS tumours,""glioblastoma,""neurosurgery,""additive manufacturing,""patient-specific implants,""3D-printed tumour models,""biomaterials in neuro-oncology,""3D-printed scaffolds," "tumour microenvironment," "personalised medicine in neurosurgery,""preoperative surgical planning,""3D-printed chemotherapy implants,""drug delivery systems in CNS tumours,""neurosurgical simulation models," and "customised cranioplasty." Additional search terms included "tumour modelling,""brain tumour reconstruction,""biofabrication for CNS tumours," "precision oncology with 3D printing,""polymer-based 3D scaffolds,""nanoparticle integration in 3D printing,""MRI-based 3D printing for neurosurgery," and "hydrogel-based 3D scaffolds."
Additional search	A manual search was performed to include references from recently published procedure-specific and disease-specific reviews. Cross-references included studies in neurosurgical innovation, biomaterial sciences, computational modelling in surgical planning, and 3D printing applications in regenerative medicine. Studies integrating biofabrication with immunotherapy and tumour microenvironment research were also explored
Sample size requirement	No strict sample size requirement

In 1986, Carl R. Deckard of the University of Texas pioneered selective laser sintering (SLS), an AM technique that greatly expanded the ability to create complex structures. Two years later, in 1988, Michal Feygin and his team developed Laminated Manufacturing (LM), an automated lamination process in which layers of material outlined by electronic files are bonded together to form complete objects [11].

In 1989, Scott S. Crump, co-founder of Stratasys, Inc. introduced fused deposition modelling (FDM), a material extrusion technique that uses polymers to build three-dimensional objects [11, 12]. In the same year, Emmanuel M. Sachs and colleagues at the Massachusetts Institute of Technology introduced an innovative 3DP method that uses conventional inkjet printer injectors to deposit binder and coloured ink onto a layer of powdered material, further expanding the versatility of AM [11]. These foundational innovations have been instrumental in shaping the advanced additive manufacturing techniques that are widely used today.

Types and functional background:

According to the 2010 American Society for Testing and Materials (ASTM) standards, AM processes are classified into seven categories: direct energy deposition, binder jetting, material jetting, material extrusion, sheet lamination, powder bed fusion, and vat polymerisation [12]. Each of these categories includes different techniques and materials. For example, binder jetting technology uses a liquid binder to selectively bond powder particles by deposition. In this process, a chemical binder is spread over the powder to form each layer, using either thermal or piezoelectric print heads. Binder jetting is known for its speed, efficiency, and precision, and is compatible with a wide range of materials, including sand, polymers, and ceramics [13, 14].

Direct energy deposition is a more complex process and is commonly used to repair or add material to existing components. Unlike material extrusion, the nozzle in direct energy deposition is not fixed to a specific axis, allowing it to move in multiple directions. It is compatible with materials such as ceramics, polymers, and metals, including combinations of metals in the form of wires or powders. Direct energy deposition can be further categorised into laser deposition and laser-engineered net shaping [14]. Material extrusion, on the other hand, involves heating materials such as metal pastes and thermoplastic polymers to a gelatinous state before ejecting them onto the print bed. This technology offers the advantage of printing with a wide range of colours and materials at a relatively low cost, with FDM being a common example that primarily uses polymers [14].

Material jetting is another AM technology, in which photopolymers are cured layer by layer under ultraviolet light to create solid structures. This process can also use wax to create polished surfaces with high accuracy [14, 15]. In contrast, sheet lamination uses layers of material to bond together and produce parts of an object, with technologies such as laminated object manufacturing and ultrasonic additive manufacturing being key examples.

Finally, powder bed fusion includes techniques such as electron beam melting, selective laser sintering, and

selective thermal sintering. These methods use an electron beam or laser to fuse materials such as metals, ceramics, or polymers into solid structures [14].

3DP software

AM begins with a specific design modelled using computer software, which generates a unique file that is then sent to a 3D printer for production [16]. Effective 3DP relies on Computer-Aided Design (CAD) and Computer-Aided Manufacturing (CAM) software. The process starts with acquiring digital data from a scanner, which is prepared using CAD software to create, analyse, and review models. This refined digital information is then utilised in the CAM stage to produce a precise 3D physical model [17, 18].

Each of these software types has different subtypes. For example, 3D Slicer, first proposed by David Gering in 1999, is a multi-channel software that uses imaging techniques to visualise patient anatomy. It allows users to combine anatomical data with functional data, providing a clear understanding of complex information. This software is used in both clinical and preclinical settings for image analysis [19]. Another example is Horos, a Digital Imaging and Communications in Medicine (DICOM) software that allows users to convert images into 3D prototypes via a 3D surface rendering option. Horos is a free tool available to Mac users [20]. Additionally, Mimics, a product by Materialise, serves as a crucial cross-checking tool in medical image processing. It is employed to assess the performance and safety of 3D modelling software by enabling users to input, process, and reconstruct images into 3D structures, ensuring the accuracy and effectiveness of the final output [21].

The molecular landscape of 3DP technology for CNS tumours; application and advantages

Role of 3DP in CNS TME

Recent advances in 3D bioprinting technology have revolutionised this technology enabling the precise placement of biomaterials and cells, allowing for the construction of complex models with heterogeneous distributions. From this perspective, bioprinted in vitro models present a flexible platform for studying tumour biology, testing drug efficacy, and developing personalised cancer therapies [22]. As a result, 3D bioprinted constructs have begun to incorporate additional elements of the tumour microenvironment (TME), such as stromal components and vasculature, thereby creating conditions that are more reflective of in vivo environments than those achievable with traditional two-dimensional (2D) and 3D cell culture systems. The potential impact of such innovations is significant, as they could greatly enhance the predictive value of preclinical cancer models and further support the development of personalised medicine in oncology [23]. Traditional 2D cultures fail to capture the complexity of tumour biology due to their inability to accurately represent both spatial and mechanical interactions. In contrast, 3D models address these limitations by precisely positioning different cell types within a 3D matrix. This approach allows for the inclusion of multiple cell types and extracellular matrix (ECM) components, offering a more comprehensive platform for personalised medicine and drug testing [24]. A study by Tang et al. highlighted how 3D bioprinting can be used to capture the biophysical heterogeneity of the TME, thereby enhancing the realism of in vitro models. By fine-tuning printing parameters and biomaterial concentrations, the researchers were able to adjust the stiffness of different regions within 3D-printed glioblastoma models, even while maintaining a constant hyaluronic acid concentration. [25] This variability in stiffness effectively replicates the distinct microenvironments observed in vivo: stiffer ECM regions promote the mesenchymal phenotype, which is linked to recurrence and poor treatment outcomes, while softer regions encourage rapid cell proliferation and support the expansion of cells with the classical phenotype [25].

Additionally, dynamically controllable microfluidic devices have been fabricated using two-photon lithography to enable the triple co-culture of endothelial cells and glioblastoma cells, providing more realistic in vitro CNS models [26]. The significance of these models lies in their ability to replicate both the luminal and parenchymal compartments of the brain, which is particularly important when assessing the ability of tumour-targeting drugs to cross the blood–brain barrier (BBB). The model demonstrated its capacity to hinder the diffusion of molecules across the BBB while allowing the passage of chemotherapy-loaded nanocarriers, making 3DP an essential tool for testing new drug delivery systems [26].

Further research using glioblastoma models has focused on developing synthetic co-cultures of Glioblastoma Stem Cells (GSCs) and glioma-associated stromal cells (GASCs) within a 3D matrix composed of alginate modified with cell adhesion peptides, hyaluronic acid, and collagen-1. This model more accurately replicates the cellular and extracellular complexity of the TME. In these 3D-printed models, GSCs exhibited enhanced resistance to chemotherapeutic drugs compared to traditional 2D models [27]. Additionally, endothelial cells integrated within the models displayed different growth patterns based on the stiffness of the surrounding ECM—showing protruding morphologies in stiffer regions and expansive growth in softer areas. The inclusion of endothelial cells also influenced drug responses in glioblastoma cells, highlighting their role in contributing to drug resistance.

These findings emphasise the potential of 3D bioprinting to model the diverse microenvironments within CNS tumours, offering valuable insights for therapeutic development [25].

In addition, studies have successfully used 3D bioprinted pediatric neural crest-derived tumors to evaluate treatment responses, demonstrating that bioprinted models better represent tumor behaviors than conventional methods. This breakthrough enables more personalized drug testing and accelerates the discovery of effective therapies specifically for pediatric CNS tumors [28].

The development of 3D bioprinted brain matrix-mimetic microenvironments using HA-based scaffolds closely simulates both the mechanical and biological properties of the human brain. Through the optimization of bioink formulations, 3D models of the TME can more accurately replicate glioblastoma cells and other CNS tumour types [29]. Over time, these 3D bioprinting techniques have become increasingly sophisticated. Recently, researchers have developed a fabricated model that almost precisely mimics the CNS TME. This model utilises an advanced bioink composed of alginate and gelatin methacryloyl. Studies using these advanced bioink models have shown that varying concentrations of gelatin within the ink significantly affect tumour cell behaviour. This highlights the potential of 3D bioprinting not only to replicate the TME but also to study the impact of various microenvironmental factors on tumour progression [29]. Such optimisation is crucial in drug testing, as it allows for the observation of drug responses in a more physiologically relevant environment compared to traditional models [23].

However, as current 3D printed models of the TME have predominantly focused on glioblastomas, future research should consider expanding these models to include other common CNS tumours, such as meningiomas. This would allow for a more comprehensive understanding of the differences within specific CNS TMEs, potentially leading to more targeted treatment options.

Studying angiogenesis and vascularization in CNS tumours

CNS tumours represent some of the most challenging cancers due to their aggressive nature and complex microenvironment, which includes a highly abnormal vascular network. GSCs are known to play a critical role in the progression and vascularisation of glioblastoma. Extrusion-based 3D bioprinting has been employed to create glioblastoma tumour models that display enhanced expression of angiogenesis-related genes [30]. These genes include *VEGF*, a key molecule in promoting blood vessel formation. *VEGF* functions by binding to *VEGFR1* and *VEGFR2* on endothelial cells, initiating a signalling cascade involving *PI3K/AKT* and *MAPK/ERK* pathways, which leads to the migration and proliferation of new blood vessels. These glioblastoma models exhibited increased stemness, closely linked to their ability to secrete VEGF and other pro-angiogenic factors [31]. These models provide a suitable scaffold for GSCs, enabling them to form spheroids and secrete higher levels of *VEGFA*, a key *VEGF* isoform that specifically binds to *VEGFR2,* leading to the formation of tubule-like structures in vitro [30].

Vascularised tumoroid models developed by Tatla et al. (2021) provide another example of how 3DP technology can be harnessed to study angiogenesis. These models were used to simulate the complex brain microenvironment, including hypoxia, a critical factor in tumour progression. Hypoxia induces the stabilisation of *HIF-1α*, which upregulates the expression of *VEGF* [32]. In the vascularised tumoroid model, primary glioblastoma cells co-localised with endothelial cells to form vascular networks, highlighting the ability of glioblastoma cells to adopt endothelial-like behaviour through direct participation in angiogenesis. This phenomenon, known as vasculogenic mimicry, allows tumour cells to contribute directly to the vascularisation process, bypassing the need for endothelial cells. This further complicates treatment options, underscoring the necessity of 3D printed models to test therapies in a viable environment [32]. Moreover, 3D modelling allows for the fine-tuning of tumour stiffness by adjusting printing parameters and biomaterial concentrations. In stiffer models, there is an upregulation of genes such as *TMEM45A* and *NDRG1*, which are associated with hypoxia-induced chemoresistance. Additionally, hypoxia-related genes including *CA IX, HIF1-α, SLC2A1* (encoding glucose transporter 1), and angiogenesis markers *VEGFA* and SPP1 were also upregulated under these conditions [32]. These findings demonstrate that 3D bioprinting can effectively mimic the stiffness of tumours, offering a more accurate representation of how angiogenesis impacts tumour behaviour.

Novel approaches using in situ 3DP to construct tissue-level cancer-vascular models have enabled precise spatial control of cancer spheroids and angiogenic structures. This precision is crucial when assessing the cancer-vascular interaction within a controlled environment. These models have revealed that the proximity of cancer cells to vascular structures significantly influences angiogenesis, particularly through the epithelial-mesenchymal transition (EMT) [33]. EMT is a process by which cancer cells acquire migratory and invasive properties, characterised by the loss of epithelial markers and the gain of mesenchymal markers such as vimentin and N-cadherin. This process is closely tied to the activation of angiogenic pathways,

where factors such as TGF-β play a pivotal role in promoting angiogenesis. Thus, 3D models have demonstrated that closer proximity to vascular structures enhances EMT and angiogenic signalling, leading to key tumour progression features such as increased vascular dysfunction and inflammation [33]. The role

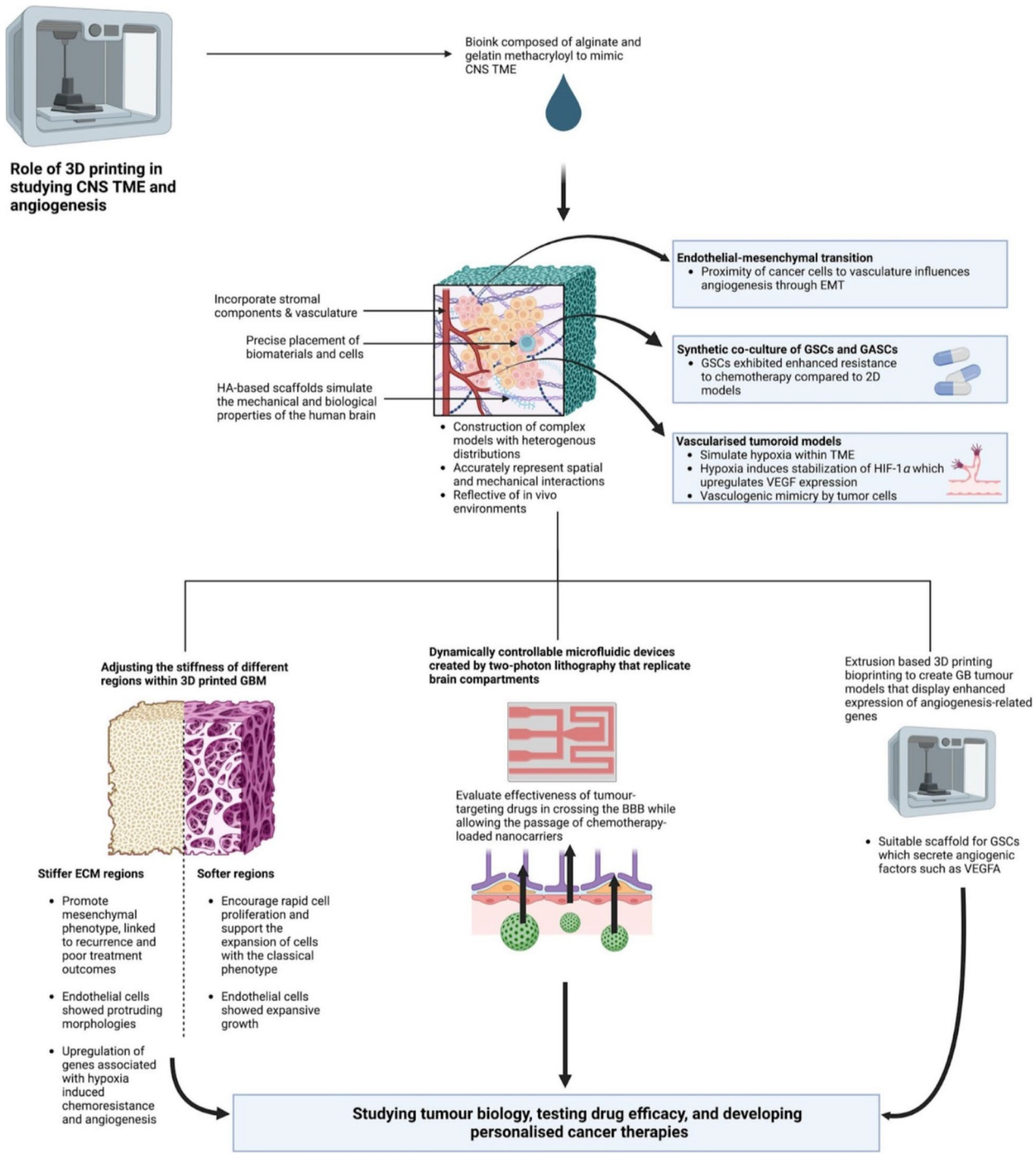

Fig. 1 The role of three-dimensional printing in the tumour microenvironment, angiogenesis and vascularisation of CNS tumours. *3D* Three Dimensional, *CNS* Central Nervous System, *TME* Tumour Microenvironment, *HA* Hyaluronic Acid, *EMT* Epithelial-Mesenchymal Transition, *GSC* Glioblastoma Stem Cell, *GASC* Glioma Associated Stromal Cell, *HIF-1* Hypoxia Inducible Factor-1, *VEGF* Vascular Endothelial Growth Factor, *ECM* Extracellular Matrix, *BBB* Blood Brain Barrier

of 3D printing in the tumour microenvironment, angiogenesis and vascularisation of CNS tumours is summarised in Fig. 1.

Modelling the cellular and genetic heterogeneity of CNS tumours

CNS tumours are complex tissues characterised by intricate interactions between various cell types [34]. Compared to 2D cultures, cells grown in 3D environments exhibit distinct cytoskeletal architecture, gene expression profiles, and metabolic activity that more closely mirror in vivo conditions [35–37]. Among CNS tumours, glioblastoma has been one of the most extensively studied using 3DP technology. Cell selection is a crucial factor in constructing 3D models that replicate cellular and genetic heterogeneity, especially for drug testing applications. Tumour cell lines, patient-derived cells, and tumour stem cells (SCs) are commonly used for this purpose [38, 39]. While tumour cell lines are frequently used, their phenotypic changes over time can make them less suitable for certain studies [38]. Several studies have utilised the commercially available U-87 MG glioblastoma cell line to develop 3D bioprinted glioblastoma models [40–42]. Other widely used cell lines include U118-MG and U251-MG [43–46]. In meningioma research, the IOMM-Lee human meningioma cell line from the American Type Culture Collection (ATCC) was employed in a study to create an accurate in vitro model of meningioma using 3D coaxial bioprinting [47].

Stem cells (SCs) are highly valuable in tissue engineering due to their ability to differentiate into various cell types, making them essential for constructing more realistic tumour environments in 3D bioprinted models. Their self-renewal capabilities and unlimited replication are directly related to tumour viability and migration [38]. Several types of SCs are used in 3DP technologies, including human embryonic stem cells (hESCs), mesenchymal stem cells (MSCs), and human induced pluripotent stem cells (hiPSCs) [48]. For instance, in a 3D bioprinted neuroblastoma (NB) model, MSCs, SH-SY5Y cells, and human primary umbilical vein endothelial cells (HUVECs) were used to prepare three different bioinks to construct the stroma, rosettes, and vasculature components of the model, respectively [49]. Neural stem cells (NSCs) can differentiate into neurons, astrocytes, and oligodendrocytes [48]. Similarly, hiPSCs, like hESCs, can be transformed into nearly any cell type within the nervous system. Incorporating various other cell types, such as endothelial cells and fibroblasts, into 3D bioprinted tumour models allows for a more accurate replication of the TME, which includes blood vessels, stromal cells, pericytes, and immune cells. This approach better mimics cellular heterogeneity and tumour behaviour [50].

The ideal in vitro growth system for tumour modelling is patient-derived cells (PDCs). Human-immortalised glioma cell lines such as U87 (Uppsala 87) and U251 have fallen out of favour due to their limited resemblance to actual glioblastoma tumour cells and the controversy surrounding their origin [51]. The most effective approach for modelling the cellular and genetic heterogeneity of tumours is to use cells obtained directly from patients. These cells are derived from surgically removed tumour tissue and can be transformed into cell lines that are cultured either as monolayers or in suspension in immunodeficient mice [52]. Recent studies have incorporated PDCs or patient-derived spheroids (PDSs) with 3DP technology to create valuable ex vivo and in vitro models. These models provide an essential tool for various applications, including target discovery, mechanistic studies of tumour biology, drug development, and personalised drug screens, all of which can aid in clinical treatment selection [25, 53–55].

Development of accurate drug testing and personalised treatment strategies

Biological 3DP allows for the precise arrangement of cells and cell–matrix materials within three-dimensional space, enabling the creation of complex tumour models in vitro. These models are instrumental in studying interactions between nerve cells and the extracellular matrix, as well as in conducting high-throughput, reproducible anti-tumour drug screenings. Such advancements facilitate accurate, personalised drug testing for individual patients. For instance, bioprinted vascularised glioblastoma models have been utilised as platforms for drug screening [41, 54, 56]. Multicellular tumour spheroids (MCTS) bioengineered on vascularised tissues exhibited similar responses when TMZ and SU were combined, mirroring the outcomes seen in U87 cells transplanted into mice [56]. These findings suggest that the microenvironment in bioprinted vascularised glioblastoma models closely parallels in vivo conditions, enabling precise drug efficacy testing [56]. In a 2019 South Korean study, researchers utilised multi-jet 3DP technology to develop a highly simulated gradient anaerobic glioma model. This model successfully replicated the in vivo structure, biochemical and biophysical properties, and the radial oxygen gradient of glioblastoma. By culturing cells from tumour patients within this model, the study found that the chemotherapy effects closely matched the actual chemotherapy responses observed in patients [57].

Another notable development includes a 3D bioprinted glioblastoma model with perfused vascular channels designed for drug screening. This model involved bioprinting a collagen layer between gelatin-based channels, where HUVECs were cultured to form a cell lining on the

inner channel surface. After 21 days of TMZ treatment, the 3D patient-derived glioblastoma spheroids exhibited a more significant reduction in metabolic activity and tumour growth compared to the 2D monolayer model. This customisable system allows for the testing of therapeutic alternatives under more physiologically relevant conditions, thereby providing deeper insights into treatment efficacy [54].

Building on the benefits of personalised models, the use of PDCs or PDSs enhances tailored treatment approaches. A study by Maloney et al. (2020) demonstrated the effectiveness of bioprinting in generating tumour organoids from patient biospecimens. In this study, bioprinted glioblastoma PTOs from two patients were treated with varying concentrations of dacomitinib or a p53 activator. Glioblastoma 1 PTOs showed a dose-dependent decrease in ATP activity with increasing doses of both drugs, whereas glioblastoma 2 organoids responded only at much higher concentrations. These results underscore tumour heterogeneity and highlight the utility of PTOs as diagnostic tools, providing empirical drug response data specific to each patient, which can guide oncologists in selecting the most effective treatment [55].

Additionally, Tang et al. (2021) demonstrated the potential of 3D bioprinted systems to enhance drug response predictions in glioblastoma. By incorporating gene expression data and drug resistance profiles from patient-derived glioblastoma cell lines into 3D models, they identified drugs that effectively target GSCs. This approach underscores the value of bioprinted 3D models in refining drug screening and optimising treatment strategies for glioblastoma [25]. Figure 2 illustrates the role of 3D printing in the development of accurate drug tests and personalised treatment strategies for CNS tumours.

The surgical landscape of 3DP for CNS tumours: application and benefits

Pre-operative planning and visualisation

One of the most critical aspects of managing brain tumours is meticulous preoperative planning [58]. Effective planning is essential for achieving successful surgical outcomes while minimising damage to surrounding healthy tissues. Accurate identification and visualisation of the tumour's location, along with mapping anatomical and functional brain areas, enables surgeons to balance tumour resection with the preservation of vital brain functions [59].

Traditional techniques such as intraoperative direct cortical stimulation (DCS) and functional magnetic resonance imaging (fMRI) have long been used in brain tumor surgery. [59] Still, they have limitations, including risks of seizures, prolonged surgery times, and challenges in integrating complex data into surgical navigation systems. While fMRI provides valuable functional data, its complexity and reliance on 2D images hinder its effectiveness. [59] In contrast, 3DP technology has revolutionised presurgical planning by creating tangible, anatomically detailed models that enhance the visualisation of the tumor and surrounding brain structures. These models allow surgeons to better understand spatial relationships and plan surgery more precisely. [59] The integration of 3DP with mixed-reality (MR) systems, like Microsoft HoloLens, further advances this by overlaying 3D MRI-derived holograms onto the patient's head in real-time, improving spatial awareness and precision during surgery. Surgeons can interact with these holograms using mid-air gestures, maintaining sterility and improving ergonomics. These innovations offer a substantial improvement over traditional methods, providing more accurate preoperative planning and enhancing surgical outcomes. [59]

Krauel et al. (2015) demonstrated the impact of 3DP in a study involving three paediatric oncology cases, including two brain tumours. Their research highlighted the significant benefits of using 3D-printed prototypes, which allowed for repeated practice and refined surgical planning. The physical models enabled surgeons to assess the tumour's characteristics and evaluate the potential resection grade more effectively [60]. By integrating diagnostic information from various imaging modalities, 3DP provides a comprehensive 3D view of the tumour, enhancing the ability to plan precise surgical interventions. In a related study, Waran et al. (2014) utilised multi material 3D-printed models to simulate brain tumour resection. These models, created from CT data, included various tissue components such as skin, bone, dura mater, and tumour. These models also enabled neurosurgeons and trainees to simulate and plan the surgical procedure, including basic steps of a craniotomy [61].

Traditional 2D imaging, such as X-rays, CT scans, and MRIs, typically provides a limited view of the anatomy and pathologies, especially in complex cases like CNS tumours. These imaging techniques often fail to capture the full extent, size, and intricate relationship of a tumour with surrounding critical neurovascular structures, making it challenging for surgeons to plan and execute precise interventions. [62] The inability to accurately visualise the tumour's shape, boundaries, and its proximity to vital structures such as blood vessels, nerves, and the spinal cord can complicate surgical planning, increasing the risk of intraoperative complications, postoperative morbidity, and suboptimal outcomes. In contrast, 3D printing technology offers a more comprehensive and detailed approach by transforming the data

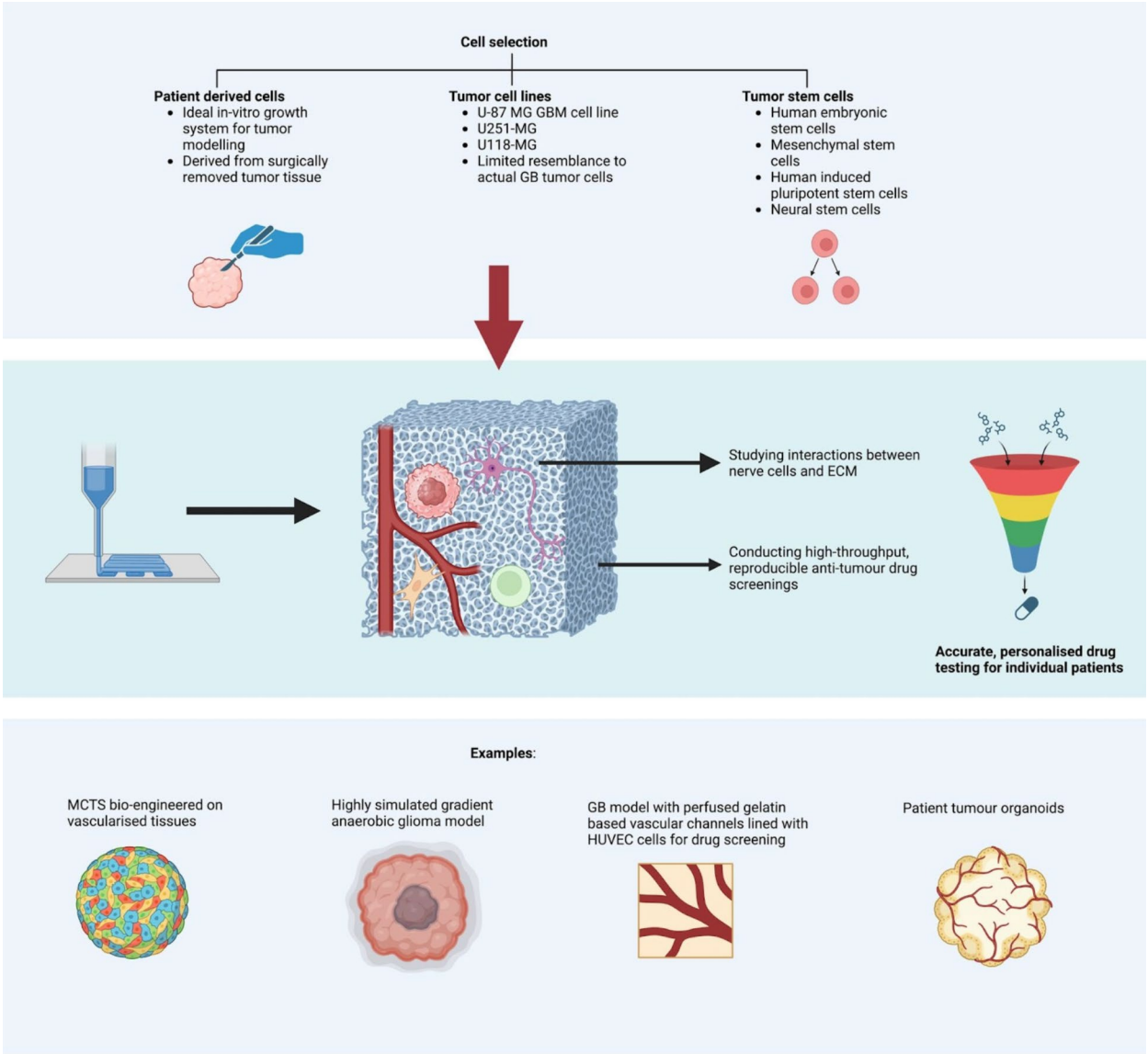

Fig. 2 The role of three-dimensional printing in developing accurate drug tests and personalised treatment strategies for central nervous system tumours. *MG* Meningioma, glioblastoma; Glioblastoma, *ECM* Extracellular Matrix, *MCTS* Multicellular Tumour Spheroids, *HUVEC* Human Primary Umbilical Vein Endothelial Cell

from CT or MRI scans into physical, tactile models. These 3D-printed models provide a more accurate representation of the tumour's size, location, and relationship with adjacent tissues, allowing for better preoperative visualisation. [62] Surgeons can examine the tumour from multiple angles and directly assess its spatial relationships, which aids in devising more personalised and precise surgical plans. The enhanced visualisation provided by 3D models enables surgeons to anticipate potential challenges during surgery, such as avoiding damage to critical structures, and to plan interventions with greater accuracy. [62] Consequently, this improved preoperative assessment leads to more effective and safer surgical interventions, potentially reducing the risk of complications and improving patient outcomes.These findings reveal that the use of 3D-printed models for CNS tumours not only enhances surgical precision but also facilitates better communication between the surgical team and the patient, fostering a clearer understanding of the procedure and its risks.

In cases such as chondrosarcomas, where complete surgical removal of the tumour is crucial due to its proximity to important neurovascular structures, 3DP has proven invaluable. Researchers have successfully used

3D-printed models to recreate the complex anatomy of these tumours, determining the precise scope of resection [63]. Additionally, 3DP has revolutionised pre-surgical planning by optimising patient positioning, tailoring surgical approaches, and guiding resections of lesions, especially those near white matter tracts and the motor cortex [64].

In addition to chondrosarcomas, studies have demonstrated that 3D printing-assisted skull base tumor surgeries allowed for better visualization of meningiomas, sellar tumors, and cerebellopontine angle tumors, reducing surgical risks [65]. Similarly, 1:1 scale 3D-printed models have to be utilized to guide the removal of a thoracic vertebral ganglioneuroma, leading to a successful outcome with minimized spinal cord damage [66]. These applications highlight 3D printing's role in reducing surgical complications and enhancing medical training, in a variety of CNS tumor types.

Recent studies provide quantitative evidence of these benefits. For example, studies have observed that in 18.8% of cases (12 out of 64 patients), neurosurgeons changed the planned extent of resection after reviewing a patient-specific 3D-printed brain tumor model, in most of these, the plan was adjusted to a more extensive tumor removal [67]. This same study found that 3D models significantly improved key surgical planning parameters compared to MRI alone: optimal head positioning and craniotomy design were achieved more accurately with the 3D prints [67].

Intraoperative assistance and postoperative care

The integration of 3DP technology into the operating room has revolutionised intraoperative precision and real-time decision-making in tumour surgery. By offering highly detailed, patient-specific models, 3DP has significantly enhanced surgeons' accuracy and confidence in navigating complex neuroanatomy [68].

Studies on these models have confirmed their use as a real-time reference for important anatomical landmarks during tumour resection [62]. The ability to hold and dissect a patient-specific model layer by layer provides the operating surgeon with a deeper understanding of the anatomy before making the first incision. The spatial depth provided by these models gives surgeons tactile feedback, allowing for precise manoeuvring [69]. As the surgeon can cross-reference the model while operating, the target areas can be clearly visualised, minimising surgical errors by ensuring that tumour resection is performed within planned margins. This reduces the likelihood of damaging critical brain structures. Additionally, in the operating room, this can lead to reduced operating time, decreased radiation exposure, and less time under general anaesthesia [70].

Moreover, 3DP has transformed the landscape of surgical implants [71]. These implants can be customised to the patient's anatomy, which is particularly useful in cases involving spinal vertebrae affected by tumours. A recent study demonstrated that using 3D-printed implants in such cases not only reduces intraoperative handling time but also significantly decreases blood loss [72]. The precision and fit of these implants lead to better surgical outcomes and quicker recovery times for patients.

Complex surgeries often involve two or more surgeons and/or trainees. In such cases, having a tangible model to discuss the next steps can facilitate better communication within the surgical team [62]. Surgeons can use these models to ensure that everyone involved has a clear understanding of the surgical plan.

Furthermore, the application of 3DP technology in postoperative care is emerging as a significant advancement in neurosurgery, offering enhanced support for patient recovery and follow-up. Studies have shown that the use of 3D-printed models in postoperative settings contributes to reduced complication rates and shorter recovery times [73, 74]. Despite these benefits, more research is needed to explore the full potential of 3DP in postoperative care. Current studies are limited, and further investigation is required to fully understand the long-term benefits, potential complications, and optimal applications of 3D-printed models and implants in postoperative care. Enhanced research efforts could provide deeper insights into how 3DP can be leveraged to improve patient outcomes and refine postoperative management strategies in neurosurgery.

Enhancing education of medical personnel, trainees and patients

Due to the complexity of CNS tumour surgery, effective hands-on training that closely replicates real-life surgical scenarios is essential. 3D-printed models facilitate clear communication and education within multidisciplinary teams, ensuring that all physicians and surgeons are thoroughly prepared for the surgical procedures and any potential complications that may arise [75]. These models enhance discussions among multidisciplinary teams by offering a clear, 3D view of the patient's anatomy, which improves communication between surgeons, radiologists, oncologists, and other specialists. This, in turn, leads to more coordinated and effective preoperative planning.

Traditional teaching methods, while invaluable, often fall short in bridging the gap between theoretical knowledge and practical application. Cadaver dissections, for example, though important, are not always feasible due to financial, ethical, and logistical constraints [76]. Additionally, cadavers lack many realistic human components,

such as hemodynamic factors [77]. The use of 2D images for visualisation, while helpful, is limited in that it does not provide the depth and spatial understanding necessary for surgery. In contrast, 3DP technology offers a solution by providing highly realistic training models that are both patient- and pathology-specific. These models offer a level of customization and depth that far exceeds what can be achieved with 2D images or even cadaveric specimens. The tactile experience of handling and practising on 3D-printed models significantly enhances the learning process, making it superior to other methods [78]. Additionally, these models are reusable and can be tailored to replicate a wide range of anatomical variations and surgical scenarios, providing invaluable hands-on experience essential for mastering complex procedures [79].

The importance of hands-on training cannot be overstated. Through repeated practice on realistic models, trainees develop the muscle memory, hand–eye coordination, and confidence necessary for successful brain surgery [80]. Simulating surgery on 3D models reduces the learning curve and better prepares trainees for the challenges they will encounter in the operating room.

Lin, et al. (2018) underscored the effectiveness of 3DP in neurosurgical training. Their study evaluated 3D models of tuberculum sellae meningiomas on neurosurgical trainees and compared their performance to those trained using traditional 2D images. [81] The findings revealed that the group using 3D models scored significantly higher on post-tests than the group using 2D materials. Additionally, trainees who worked with 3D models reported greater interest in learning and an improved understanding of surgical views [81]. As medical technology continues to evolve, 3DP is expected to play a critical role in preparing the next generation of skilled neurosurgeons.

Beyond surgical planning, doctor-patient education also benefits from 3DP, as these models can serve as a basis for explaining the surgical approach, benefits, and potential complications to patients. This helps patients visualise the tumour and understand their condition better. Patients diagnosed with brain tumours often struggle to grasp the complex medical information presented to them. Traditional 2D MRI and CT scans can be difficult for patients to interpret, leading to increased anxiety and confusion about their procedures [82]. To address this, clinicians have introduced 3D brain tumour modelling (3DBTM) in neuro-oncology clinics. Patients reported an 85% increase in understanding of the procedure when 3D models were used compared to traditional 2D images. 3DBTM also led to more informed patient decision-making, reducing uncertainty around complex procedures [82]. The use of 3DP in patient education not only improves procedural understanding but also plays a role in enhancing shared decision-making between patients and clinicians. Exploratory studies on the use of 3D-printed models for patients with glioma found that these models not only improved medical understanding but also enabled patients to be more involved in decisions regarding their treatment [83]. The tangible presence of a model of their tumour encouraged patients to ask more informed questions, leading to meaningful discussions with their neurosurgeons. However, a potential drawback was noted, as some patients found these models emotionally confronting, particularly when presented with a serious neurological pathology for the first time. Therefore, caution should be exercised regarding the timing and manner of integrating these tools [83].

Challenges with 3DP in CNS tumour applications

Material biocompatibility and costs

One of the primary challenges in 3DP is selecting the appropriate material. The ideal material must be biocompatible and meet the mechanical and functional requirements of living tissues. Currently, natural and synthetic polymers are the most commonly used materials. While natural polymers offer excellent biocompatibility, they often have suboptimal mechanical properties [84]. Conversely, synthetic polymers typically provide superior mechanical strength but may not fully mimic the characteristics of neural tissue [85]. Even with advances in polychromatic materials, achieving an accurate representation of neural tissue remains elusive. Despite significant progress in 3DP technology, creating soft tissue structures continues to be a challenge. This is particularly crucial in neurosurgery, where a combination of hard and soft materials is necessary to effectively replicate both the skull and neural tissue [10].

Beyond material selection, simulating the hemodynamic processes of the human body presents a significant challenge. For instance, Lin et al. employed 3DP for skull base tumours surgery, but their models fell short of recreating the dynamic flow of cerebrospinal fluid and blood typically observed in such procedures. [86] These dynamic processes are essential for accurate surgical planning and successful outcomes.

Compounding these technical challenges is the issue of cost. The initial investment in 3D printers can range from hundreds to thousands of dollars, and additional expenses include labour costs for technicians and engineers, as well as training costs for staff [87]. The high-quality biocompatible materials required for 3DP, including specialised polymers, metals, and composites for neurosurgical implants, further increase production costs [88]. These expenses significantly impact accessibility in many resource-limited settings. For example,

producing a single anatomical model can exceed $2,000 USD, a prohibitive amount for most healthcare systems in low and middle-income countries (LMICs). In Pakistan, while the national health system covers many neurosurgical procedures, it does not extend to 3D-printed implants made from materials like polyetheretherketone (PEEK) or titanium. Consequently, neurosurgeons often use free-hand polymethylmethacrylate (PMMA) for cranioplasty, a much cheaper alternative, though it generally results in inferior clinical outcomes compared to 3D-printed implants [89]. Similarly, in India, the use of PMMA is widespread due to financial constraints [90]. Additionally, imaging modalities such as MRI and CT scans, required to generate data for 3DP, further add to the overall cost as they are not interchangeable [91].

Technical challenges and biological complexities

A significant limitation of 3DP in CNS tumour research lies in its inability to fully replicate the complex architecture of the tumour environment. While the technology allows for precise cell and biomaterial placement, it often struggles to recreate the heterogeneity of in vivo tumours. This challenge is evident in attempts to replicate the interactions between tumour cells and the ECM, as well as in the fabrication of vascularised tumour models [24, 92]. Current models often lack the functional and structural integrity of natural vasculature, leading to incomplete nutrient and oxygen delivery, which are crucial for tumour maintenance. Furthermore, these models frequently fail to capture the biophysical and biochemical cues essential for tumour angiogenesis. Elements such as matrix stiffness, shear stress, and interstitial flow are difficult to reproduce with current technology, leading to endothelial cell behaviour that is skewed towards a more superficial model framework [33].

The biological complexity of the CNS TME further complicates the application of 3DP. Current models often oversimplify interactions between various cell types, primarily focusing on endothelial and tumour cells while neglecting the roles of neurons, astrocytes, microglia, and immune cells [26]. This simplification can result in inaccurate representations of the TME, impacting the evaluation of drug delivery mechanisms. Additionally, the ECM in these models is often oversimplified, lacking the diverse components necessary for accurately mimicking tumour-ECM interactions [27]. This oversimplification, coupled with the high degree of cellular heterogeneity, particularly in glioblastoma models, makes it challenging to reproduce consistent results across studies [93, 94].

Efforts to replicate tumour vascularisation have also faced significant challenges. The heterogeneity of endothelial cells is particularly difficult to reproduce, as tumour endothelial cells often exhibit distinct genetic profiles compared to normal endothelial cells, influencing their response to pro-angiogenic signals. Various 3D models, including tissue-engineered constructs and organ-on-chips, have been developed to better mimic tumour vasculature [94]. These models have demonstrated that angiogenesis within CNS tumours is driven not only by VEGF but also by the Notch, Wnt, and integrin pathways. Moreover, these models highlight the importance of considering the spatial and temporal dynamics of genetic signalling, as the TME is constantly evolving. Changes in the vascular network can ultimately affect treatment outcomes [94]. These models could be utilised to screen anti-angiogenic therapeutics, providing a valuable tool for preclinical testing of new cancer treatments [25].

Additionally, the bioprinting of capillaries remains largely constrained by the resolution and speed limitations of current bioprinters [95]. Brain capillaries typically range from 7 to 10 μm in diameter, while extrusion-based and droplet-based bioprinters have a maximum resolution of around 50 μm due to nozzle and inkjet head limitations [96, 97]. Although acellular biomaterials can achieve finer resolution, incorporating high cell densities into bioinks requires larger nozzles to preserve cell viability, reducing resolution to between 200 and 500 μm. Light-based 3D bioprinters also face resolution challenges, with light scattering from cells causing the resolution to range from tens to hundreds of micrometres. Achieving high resolution ($\leq$50 μm) with high cell density ($\geq$20 million cells/mL) in complex models remains a significant hurdle [97]. Recent advancements, such as DLP-based 3D bioprinting combined with iodixanol to reduce light scattering, have successfully produced vascular channels with diameters between 250 and 600 μm at high cell densities (40 million cells/mL). However, creating capillaries remains difficult due to the extended printing times required, which negatively affect cell viability [97].

Ethical, privacy and accessibility issues

The ethical landscape surrounding 3DP is complex and demands careful consideration. With the advent of innovative technologies, obtaining informed consent has become more challenging, as patients need to be familiarised with these advances [98]. This requires additional time and resources to educate patients about the technology's benefits and its implications for their surgical procedures [99].

The use of medical imaging data for 3DP introduces further complications related to privacy and security regulations [10]. The segmentation process in brain tumour imaging is often automated through ML-based algorithms, further complicating the ethical landscape [67].

Ensuring data privacy requires robust protection mechanisms, particularly when patient-specific details are digitised and stored [100]. Additionally, securing regulatory approval for 3D-printed medical devices presents its own set of challenges. These include the complexity of classifying such products, managing unique risks associated with living cells, ensuring consistent quality, and addressing manufacturing challenges such as sterility and biocompatibility [101].

Lastly, ensuring equitable access to 3D modelling technology, particularly in LMICs, remains a significant challenge due to cost and other ethical considerations. Not all healthcare facilities possess the resources or expertise to implement this technology, potentially leading to inequalities in patient care [10].

Personnel demands and procedural delays

Timely and precise interventions are crucial for successful brain tumour therapies. The importance of precision is heightened by the intricate anatomy of the brain, where even slight misinterpretations can lead to serious surgical errors [67]. This challenge is further compounded by the frequent occurrence of artefacts in MRI and CT scans, underscoring the need for improved image processing techniques [102]. Effectively utilising advanced technologies such as 3DP requires a multidisciplinary approach involving physicians, surgeons, radiologists, technicians, and other healthcare professionals [99].

However, integrating 3DP into surgical planning necessitates adjustments to established routines, which may disrupt traditional surgical schedules and procedures, potentially leading to procedural delays [103]. Additionally, incorporating accurate 3D stereotactic reconstructions often requires extensive data processing, analysis, and decision-making. This can further delay surgical planning, especially in emergency situations [104–107].

Discussion and prospects

Providing low cost 3DPs and improving accessibility in resource-limited settings:

Resource-limited settings often face considerable challenges, including inadequate infrastructure and limited resources, which significantly hinder the delivery of critical care [108]. However, this situation is beginning to change with the advent of low-cost 3DP technology. In a notable pilot study, Sidabutar et al. (2023) explored the use of entry-level, low-cost 3D printers in various neurosurgical cases, including skull base tumours. Their findings were significant, demonstrating that these models were up to 233 times more cost-effective than those produced in earlier studies using high-end printers, although this advantage came at the cost of longer printing times [109]. Such advancements have the potential to revolutionise healthcare in LMICs.

Some models suggest that if medical facilities have their own 3D printers and trained technicians, an in-house operator can provide immediate access to the necessary equipment. However, the high costs associated with this approach have led many hospitals to rely on independent operators who offer external printing services. This method is more cost-effective but requires careful and timely coordination. Additionally, clinics and hospitals that achieve the most efficient price-possibility frontier often utilise printer farms, where a single company operates multiple printers in a central location, offering both cost efficiency and timely service delivery [110]. These advancements could significantly impact healthcare in LMICs.

3D-printed neurosurgical models have been found to be cost-effective, with an average manufacturing cost per model of $624.83 USD [111]. Moreover, some streamlined processes can reduce the cost to as low as $3–4 per brain hemisphere, making 3D printing a more accessible alternative to traditional imaging-based surgical planning [112]. Additionally, studies indicate that using 3D-printed models for preoperative planning significantly improves surgical outcomes, reduces surgical time, and ultimately lowers hospital costs [113].

Addressing technical, ethical, privacy and safety concerns

The integration of 3DP in medicine presents both technical and safety challenges, necessitating stringent regulations by governing bodies such as the FDA [114]. These issues must be addressed before 3DP can be routinely incorporated into clinical practice. Collaboration between academia, the FDA, and the medical industry is essential to ensure patient safety, particularly when using FDA-cleared software and hardware for complex cases [115]. A critical aspect of this collaboration is ensuring the biocompatibility of materials to prevent serious complications, with ongoing research into advanced biodegradable materials playing a pivotal role in enhancing the safety of 3DP [116]. Additionally, due to privacy concerns associated with 3DP, robust guidelines must be established to secure patient data [117]. To address legal concerns, 3DP companies will need to revise copyright agreements and develop stronger codes of conduct [118]. Furthermore, it is crucial to implement regulations on the turnover and commercialisation limits for 3D bioprinting technologies involving human organs and tissues, alongside establishing penalties for the illegal trafficking of artificial organs, to ensure ethical practices in this emerging field [119]. The full potential of this technology can be responsibly harnessed once unified protocols

and standardised training programmes are mandated by authorities [120].

New developments

Enhancing 3DP with AI

Artificial intelligence (AI) has significantly enhanced 3DP by improving image processing, precision, and quality. Machine learning and deep learning have streamlined the manufacturing process by aiding in decision-making and reducing real-time order errors [121]. AI also supports pharmaceutical 3DP by automating traditional methods and lowering costs [122, 123]. Additionally, AI improves 3DP by automating the design and manufacturing processes of drug delivery systems. For instance, AI models can predict key manufacturing parameters and optimise drug release profiles. This advancement streamlines the production of personalised medicines and diminishes reliance on traditional trial-and-error methods [122]. Moreover, AI is enhancing the accuracy and efficiency of 3D bioprinting, particularly in tissue engineering and surgical planning. Deep learning algorithms enable real-time monitoring and correction of anomalies during the bioprinting process, which is crucial for creating complex tissue structures with high precision [124]. AI also facilitates the development of smart biomaterials that can dynamically respond to environmental stimuli, thereby improving the functionality and integration of 3D-printed medical devices. This includes optimising the design of these materials to ensure they meet specific medical requirements [123].

Advancing into 4DP technology

Four-dimensional printing (4DP) integrates smart materials into the printing process, enabling them to change shape, function, and properties in response to environmental factors. This represents a significant advancement over the static 3DP materials currently in use. The technology is particularly valuable in producing advanced medical devices, including self-healing implants. The dynamic nature of 4D-printed materials also enhances manufacturing efficiency and conserves materials by reducing waste [123, 125, 126]. As 4DP represents the future of manufacturing in healthcare, we can expect to see more dynamic and adaptive solutions compared to those currently offered by 3D models. As research and development progress, more sophisticated applications are likely to emerge, including smart implants that can respond to biological signals. The continuous improvement of 4DP applications holds significant potential to advance patient care and reduce the need for invasive procedures [127, 128].

Study limitations

A significant limitation of this review is the reliance on case series with relatively small sample sizes for evaluating 3DP techniques in CNS tumours. The limited number of cases may not fully represent the broader patient population, thereby impacting the generalisability of the results. This constraint makes it challenging to draw definitive conclusions about the effectiveness and applicability of 3DP technologies across various types of CNS tumours. To address this issue, future research should aim to include larger and more diverse patient cohorts to enhance the validity and applicability of the findings.

Additionally, some data and insights regarding tumour-specific applications were extrapolated from studies focused on non-tumour-based neurosurgeries. This extrapolation introduces a potential mismatch between the models used and the specific requirements of CNS tumours, potentially leading to less accurate or relevant conclusions for tumour applications. Moreover, the studies reviewed were conducted in a landscape where different research groups employed a variety of software and 3DP systems, reflecting a notable lack of standardisation in the field. The variability in technologies and methodologies across studies introduces significant variability, which can affect the comparability and reproducibility of results. Establishing standardised protocols and technologies would enhance the reliability and interpretability of future research. Additionally, fostering collaboration between research groups to develop consensus guidelines could further enhance reproducibility and improve the overall quality of evidence in this field.

Most studies that explored the application of 3DP technology have primarily focused on glioblastomas. This narrow focus underscores the need for further research into other types of CNS tumours, such as meningiomas, medulloblastomas, and ependymomas, to better understand the technology's broader applicability. Expanding research to include a wider range of tumour types would provide a more comprehensive view of how 3DP can be utilised across different CNS tumour contexts. The current literature on the application of 3DP in CNS tumours is quite limited, making it challenging to thoroughly analyse both its current use and future potential. This scarcity of research hampers our ability to fully understand the benefits and limitations of 3DP technologies in the context of CNS tumours. The limited number of studies on 3DP applications in CNS tumours may also be influenced by the technology's current limitations and accessibility, which tend to be concentrated in high-income countries. This geographic and economic disparity can restrict the widespread adoption and exploration of 3DP technologies, particularly in lower-income regions where such innovations may not be as readily available.

Furthermore, most studies have utilised commercially available cell lines, such as U-87 MG, U118-MG, and U251-MG, for research on 3DP applications. While useful, these cell lines do not fully capture the complex behaviour of tumours in actual patients. Consequently, drug testing data derived from these cell lines may not accurately reflect the clinical realities of tumour behaviour or treatment responses.

Conclusion

In conclusion, 3DP holds transformative potential for the medical and surgical management of CNS tumours. The technology offers significant advancements across preoperative planning, intraoperative guidance, and medical education by enabling the creation of highly accurate, patient-specific models. These models enhance visualisation and understanding of complex tumour structures, contributing to improved surgical outcomes. Despite its promising capabilities, 3DP faces limitations such as long printing times, inaccuracies in printing and quality. Addressing these limitations and to fully realise the potential of 3DP in treating CNS tumours, more targeted research is needed to develop and validate techniques specific to various tumour types. One promising area for exploration is 4D technology, which could introduce dynamic elements to the otherwise static 3D models. Tapping into these areas will enhance the effectiveness and precision of 3DP in neurosurgery, ultimately benefiting surgeons, trainees, oncologists, and, most importantly, patients.

Abbreviations

3DP	3-dimensional printing
CNS	Central nervous system
WHO	World Health Organisation
AM	Additive manufacturing
SLS	Selective laser sintering
SLA	Stereolithography apparatus
LM	Laminated manufacturing
FDM	Fused deposition modeling
ASTM	American society for testing and materials
CAD	Computer aided design
CAM	Computer aided manufacturing
DICOM	Digital imaging and communications in medicine
TME	Tumour microenvironment
ECM	Extracellular matrix
HA	Hyaluronic acid
BBB	Blood brain barrier
GSC	Glioblastoma stem cell
GASC	Glioma associated stromal cell
VEGF	Vascular endothelial growth factor
PI3K	Phosphatidylinositol 3-kinase
AKT	Ak strain transforming
MAPK	Mitogen-activated protein kinase
ERK	Extracellular-signal-regulated kinase
EMT	Epithelial-mesenchymal transition
TGF-B	Transforming growth factor-beta
MG	Meningioma
ATCC	American type culture collection
SC	Stem Cell
hESC	Human embryonic stem cell
MSC	Mesenchymal stem cell
hiPSC	Human induced pluripotent stem cell
NB	Neuroblastoma
HUVEC	Human primary umbilical vein endothelial cell
NSC	Neural stem cell
PDC	Patient derived cells
PDS	Patient derived spheroid
PTO	Patient derived tumor organoid
ATP	Adenosine triphosphate
DCS	Direct cortical stimulation
fMRI	Functional magnetic resonance imaging
3DBTM	3-dimensional brain tumor modelling
MRI	Magnetic resonance imaging
DLP	Digital light processing
ML	Machine learning
CT	Computer tomography
PPF	Price-possibility frontier
FDA	Food and drug administration
AI	Artificial intelligence
MTCS	Multicellular tumour spheroids
TMZ	Temozolomide
SU	Sulfonyurea

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Consent for publication

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Competing interests

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