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Review article

Application of three-dimensional (3D) bioprinting in anti-cancer therapy

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ABSTRACT

Three-dimensional (3D) bioprinting is a novel technology that enables the creation of 3D structures with bioinks, the biomaterials containing living cells. 3D bioprinted structures can mimic human tissue at different levels of complexity from cells to organs. Currently, 3D bioprinting is a promising method in regenerative medicine and tissue engineering applications, as well as in anti-cancer therapy research. Cancer, a type of complex and multifaceted disease, presents significant challenges regarding diagnosis, treatment, and drug development. 3D bioprinted models of cancer have been used to investigate the molecular mechanisms of oncogenesis, the development of cancers, and the responses to treatment. Conventional 2D cancer models have limitations in predicting human clinical outcomes and drug responses, while 3D bioprinting offers an innovative technique for creating 3D tissue structures that closely mimic the natural characteristics of cancers in terms of morphology, composition, structure, and function. By precise manipulation of the spatial arrangement of different cell types, extracellular matrix components, and vascular networks, 3D bioprinting facilitates the development of cancer models that are more accurate and representative, emulating intricate interactions between cancer cells and their surrounding microenvironment. Moreover, the technology of 3D bioprinting enables the creation of personalized cancer models using patient-derived cells and biomarkers, thereby advancing the fields of precision medicine and immunotherapy. The integration of 3D cell models with 3D bioprinting technology holds the potential to revolutionize cancer research, offering extensive flexibility, precision, and adaptability in crafting customized 3D structures with desired attributes and functionalities. In conclusion, 3D bioprinting exhibits significant potential in cancer research, providing opportunities for identifying therapeutic targets, reducing reliance on animal experiments, and potentially lowering the overall cost of cancer treatment. Further investigation and development are necessary to address challenges such as cell viability, printing resolution, material characteristics, and cost-effectiveness. With ongoing progress, 3D bioprinting can significantly impact the field of cancer research and improve patient outcomes.

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1. Introduction

Currently, 3D bioprinting is emerging as a promising technology that enables the fabrication of 3D tissue constructs, cell-laden scaffolds, and organoids using biocompatible materials and living cells. It has the potential to revolutionize the investigation and development of tissue engineering and regenerative medicine by providing a novel approach to creating 3D models that mimic the structure and function of native tissues and organs [1]. The application of 3D bioprinting extends to diverse fields of basic and clinical medical research. Among them, cancer research is one aspect with promising outcomes, through creating realistic models of tumors for drug discovery, screening, and personalized treatment [2]. Tocchio et al. used 3D cell models to simulate the microenvironment and cell-cell interactions of tumors *in vivo*, while using magnetic permeability self-assembly technology to achieve coding and high-throughput (HTP) assembly methods for different cell types, providing a more accurate and reliable model for cancer research and contributing to a deeper understanding of cancer development and metastasis mechanisms. It provides a new approach for drug development and therapeutic strategy development [3].

Cancer, a heterogeneous and multifactorial disease characterized by abnormal proliferation and invasion, is becoming one of the major health challenges worldwide, accounting for millions of deaths every year [4]. Despite advances in cancer diagnosis and treatment, there remains an urgent need for more effective, less toxic therapies with specific targets in different types of cancers. However, traditional tumor models, such as 2D cell cultures and animal models have a shortcoming in predicting human clinical outcomes, and the success rate of anticancer drugs entering clinical trials and obtaining marketing approval is less than 10% [5,6]. By reducing the reliance on animal experiments, 3D bioprinting plays a crucial role in minimizing animal research and addressing related ethical concerns. Traditional cancer research often relies on 2D cell models and animal models, but these approaches are limited by ethical and legal considerations and often fail to accurately predict clinical outcomes in humans, for example, species differences and the low success rate of drug clinical trials [7–9]. Therefore, it is imperative to develop a highly precise and customizable model of human tissue to alleviate ethical concerns and offer more dependable and representative alternatives.

Inspiringly, 3D bioprinting offers a promising solution to this problem by creating 3D tumor models that closely resemble natural tumors in terms of morphology, composition, structure, and function. This review focused on 3D bioprinting, a useful tool for 3D realistic models of tumors, providing more accurate and relevant information for cancer therapy with personalized medicine.

1.1. The 3D cell culture is a promising method in cancer research

Diverse human tissues are complex 3D structures, as well as different types of cancers, which are composed of heterogeneous cell populations, including heterogeneous cancer cells and a variety of non-cancerous cells, such as stromal fibroblasts, immune cells, and epithelial cells, while the non-cellular part includes extracellular matrix (ECM) and secretory factors (Fig. 1). Meanwhile, the tumor microenvironment (TME) is complex because of the interaction between cancer cells themselves and with other cell types embedded in the heterogeneous ECM [10,11], vascularization is also an important factor for tumor growth in the microenvironment [12].

Currently, the exploration of the molecular mechanism of tumor cell motility relies on two-dimensional (2D) cell models, which have been used to assess drug sensitivity and HTP screening of drugs [13,14]. However, the complexity and diversity of the TME or accurately predict drug response in such models are limited, which leads to a lack of efficacy in clinical trials [5,15,16]. 3D cell models

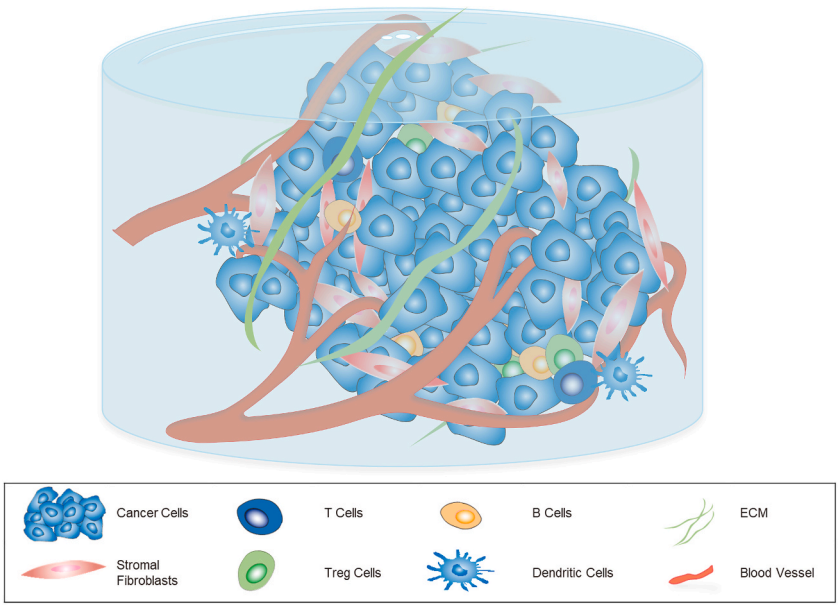

Fig. 1. The schematic diagram of the interaction between cancer cells and their surroundings.

have been utilized in tumor research to enhance the comprehension of tumor genesis and developmental mechanisms. For instance, migration and invasion constitute vital attributes of tumor cell development and metastasis. 2D cell culture predominantly portrays the behavior of individual cells; however, within 3D cell culture, the phenomena of both collective invasion and cell necrosis manifest. This association might be more closely linked to the intricate interplays among diverse cells within the organism, including cell-cell adhesion, cell-matrix interactions, and the like [17,18]. Importantly, the development of 3D cell models can maintain cell differentiation and interaction, especially from 2D cell models regarding gene expression, signaling pathways, cellular morphology, proliferation, motility, and drug sensitivity [3,19–24]. Chen et al. revealed the presence of various proteins and peptides in 3D cell models [12], which could demonstrate the feasibility of bioinks to fabricate cell-loaded constructs, and that the energy storage modulus and loss modulus remain stable when the bioinks are subjected to a small range of oscillatory strains; however, these moduli decrease rapidly once oscillatory strains of more than 0% are exceeded. In summary, 3D cell models can mimic the key properties of TMEs. In summary, the 3D cellular model can simulate the key properties of the TME, including the composition and modulus of the ECM and the multicellular spheroidal structure [12].

Lee et al. first reported the protein profiling in a 3D cell model of ovarian cancer [25], which has been developed as a powerful *in vitro* model of human development and disease, including cancer research, called organoids [26]. Soon, the application of organoids extends to diverse types of epithelial malignancies, through implanting patient-derived cells (PDC) into a semi-solid cell matrix with a growth factor-rich medium, requiring a variety of different scaffold and matrix components for different cancer sources [27]. Organoids, as 3D cell models, preserve the heterogeneity of tumor cells and enable the reconstruction of the endogenous structure of its original tissues, which closely resembles the *in vivo* tumor environment, even maintaining the same driver mutations identified in primary tumors from patients [28,29]. Overall, 3D cell models can reflect the heterogeneity and diversity of tumors within and between different patients, even with the same types of cancer, which is critical for personalized medicine treatment.

Since then, the methods for producing multicellular spheroids have been developed rapidly. For example, the forced-floating methods have become the most popular one, which employs non-adherent surfaces to facilitate cell-cell interactions to form spheroids [30]. Another method is based on agitation to avoid the adhesion of tumor cells to the vessel walls [31,32]. In 3D cell models, the volume and shape of microsphere formation will affect the sensitivity to the environment, as well as the ECM associated with the microsphere [33]. The cell-cell and cell-ECM interaction in 3D cell models can facilitate the investigation of physiological and pathological processes in the development of cancer [34], so incorporating 3D culture approaches for ECM are necessary for further investigation [35,36].

However, common 3D cell models have some limitations that 3D bioprinting models can overcome. For example, methods like forced-floating and agitation might lead to uneven cell and nutrient distribution, low reproducibility, and limited scalability. Indeed, 3D cell culture technologies have been able to advance with developments in the fields of cell biology, bioengineering, and biomaterials, which include organoids, multicellular spheroids, and 3D bioprinting [26,30,37]. However, to better mimic tissue morphology, function, and microenvironment, 3D bioprinting has been more groundbreaking, allowing precise control of the spatial organization of cells and materials used to accurately replicate functional tissue units to create organoids for screening drugs and vaccines or *in vitro* disease models [38,39].

In addition, the generation of bioinks has advanced 3D printing technology by offering great possibilities for 3D bioprinting of tissues or organs, and it has been shown that 3D-printed multicellular spheroids can characterize necrotic cores and drug-resistant phenotypes of epithelial solid tumors [40], and bioinks can be customized according to the unique attributes of a variety of tissues and organ [41]. In the field of life sciences, bioinks are widely used in the construction of *in vitro* tissue models [12,42], and are applied in several clinical studies [43], moreover, studies have been conducted to reveal the considerable promise of 3D printed drugs, decellularized ECM scaffolds, simple 3D printed tissues, and 3D printed lungs, heart valves, skin, ear cartilage, and other organs [44–46], and 3D bioprinting is predicted to clinical translation within the next decade [47], which will bring improvements to patients' conditions and even save lives.

For this purpose, 3D bioprinting exhibits enormous advantages in constructing the *in vitro* 3D cell culture model meeting the complex criteria *in vivo*, which are often fraught with challenges [48].

1.2. 3D bioprinting facilitates the research with 3D cell culture

3D printing technology creates complex 3D structures with predefined shapes, while with bioink (biomaterial matrix mixed with cells), 3D bioprinting conducts a process of depositing biological materials and cells layer-by-layer from computer-aided designs and co-cultures carriers with 3D structures of different material matrices [37,49]. Such cells can grow and migrate in the 3D spatial structural carrier, constituting a 3D cell-carrier matrix complex [50]. Accordingly, when building 3D cellular tumor models, 3D bioprinting technology offers new ideas for customized, high-resolution, reproducible, and tunable 3D cellular models using ECM mimics or other bioinks combined with cells [51]. Utama et al. designed a bespoke drop-on-demand 3D bioprinter in HTP of 3D multicellular spheroids embedded inside a hydrogel matrix with precise control over size and cell number [52], opening up many opportunities, in particular, the possibility of incorporating mixtures of primary cells and stem cells, which facilitates the exploration of precision and regenerative medicine. With 3D bioprinted cell culture models, it is facilitated to identify and screen new anti-cancer drugs, analyze their cellular toxicity, and develop precision drugs. Multiple features of TME contained by 3D bioprinted cancer models represent cancer progression and migration, emerging as useful methods for the investigation of cancer metastasis and drug screening [53].

Compared with traditional 3D cell culture methods, 3D bioprinting takes the advantages of high resolution, reproducibility, scalability, automation, and customization [54,55]. HTP 3D printing manufacturing platforms enable rapid and efficient preparation

of various types of 3D cell models that are tailored to specific research purposes by adjusting the composition, geometry, architecture, and function of bioprinted structures [56–58]. In addition, 3D bioprinting allows the integration of multiple cell types and bioactive bioinks to create more complex and dynamic 3D cell models encapsulating epithelial-mesenchymal transition (EMT) [59,60]. During the 3D bioprinting process, the choice of bioinks is very important. By comparing three hydrogels in breast cancer and melanoma cells, Schmid et al. found that different types of cancer have diverse cellular responses on mechanically and biologically different bioinks, even different cell lines in the same cancer type [61].

It has been validated that 3D cell models from PDC enable drug sensitivity for special patients by providing a more realistic and representative platform for examining drug efficacy [62,63], playing an important role in the investigation of anti-cancer therapy. 3D bioprinting technology has facilitated the development of 3D cell models by providing a high degree of flexibility, precision, and versatility in creating custom 3D structures with desired properties and functions. The combination of 3D cell models and 3D bioprinting technology has great potential to advance cancer research and improve anti-cancer treatments (Fig. 2).

1.3. The application of 3D bioprinting in malignancies

1.3.1. Brain tumor

Glioma is a mixed solid tumor with neoplastic and non-neoplastic components with high malignancy, recurrence rate, and chemoresistance. The interaction between glioma cells and their TME is directly performed through cell-to-cell mediated by surface molecules, or indirectly conducted through apocrine or paracrine signaling mediated by cytokines and growth factors [64]. However, combining 3D bioprinting and neural cells remains a big challenge currently. To solve this problem, different materials have been developed. Among them, gelatin (GEL) is widely used in tissue engineering due to its high biocompatibility, sodium alginate (SA) maintains cell viability with steeliness, while Pluronic F-127 is a kind of surfactant usually used to modify material properties [65] (Fig. 1).

In 2018, van Pel et al. compared complementary approaches, 3D bioprinting and scaffold-free 3D tissue culture, and found that 3D tissue culture for organoid development has broad accessibility to facilitate the examination of invasion using different neural progenitor cells [66]. Focused on the special subtype cells in glioma, Dai et al. established a 3D bioprinted glioma stem cell (GSC) model with modified porous GEL/alginate/fibrinogen hydrogel to mimic ECM, which increased the survival rate and efficient proliferation of GSC. The maintenance of GSC characteristics in this model along with its differentiation potential to vessels, suggests a novel alternative tool for the investigation of gliomagenesis, GSC biology, and its sensitivity [50]. Soon, Wang et al. also confirmed the GSC enrichment in a 3D bioprinted tumor model and predicted EMT as the molecular mechanism for improved stemness properties [67]. The same research groups verified that bioprinting GSC improved vascularization potential *in vitro* with increased angiogenesis-related gene expression and vascular endothelial growth factor (VEGF) secretion, providing a suitable TME for glioma cells and GSCs [68,69]. Dai et al. promoted 3D bioprined glioma models into a custom-made coaxial extrusion 3D bioprinting system to construct self-assembled multicellular heterogeneous brain tumor fibers. The CRE-LOXP switch gene system confirmed the tumor-stromal interaction significantly [70]. To address the increased risk of contacting wells in HTP multiple plates, Clark et al. developed organoid immersion bioprinting methods with hyaluronic acid (HA) print baths, in which organoids are bioprinted into support baths in well plates. In patient-derived organoids (PDO) from glioma biospecimens, this optimized immersion bioprinting approach showed a general dose-dependent response to p53 activator and temozolomide (TMZ), which is the most used drug in brain tumors [71].

As the most malignant type of glioma, glioblastoma (GBM) is a major reason for poor survival of patients with brain cancer, with invasive characteristics and infiltration into brain tissues, which will influence neurons [72]. Neufeld et al. created fibrin GBM bioink

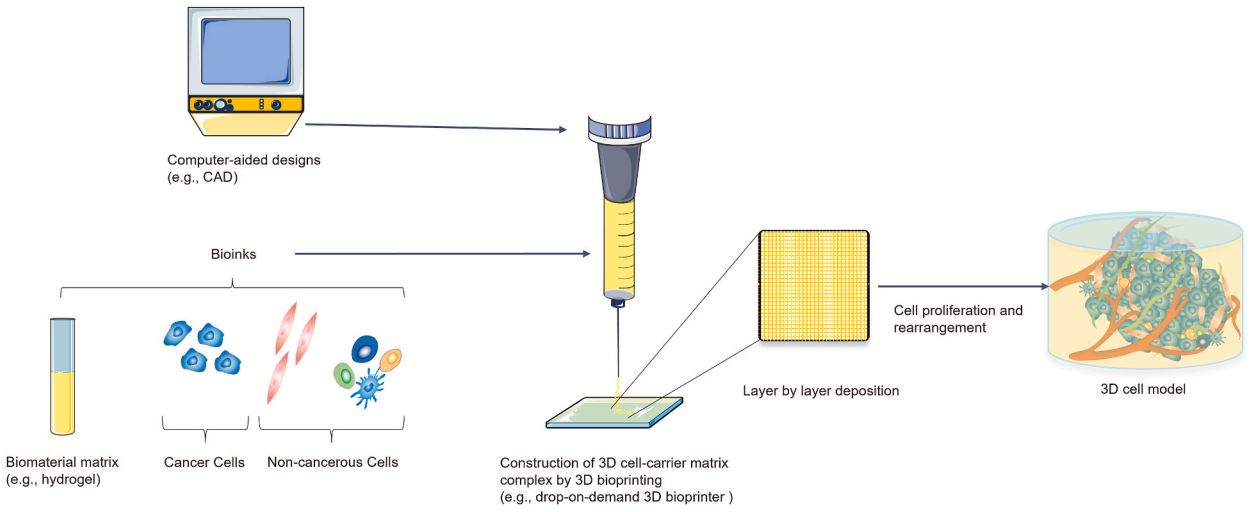

Fig. 2. The process of 3D bioprinting for 3D cell culture models.

consisting of patient-derived GBM cells, astrocytes, and microglia to recapitulate the heterogenic TME along with perfused blood vessels. This 3D bioprinted GBM model showed powerful potential for target discovery, therapy screening, and drug development, compared with 2D culture and animal models [73].

Tang et al. compared the growth of stem cells in GBM alone or with astrocytes and neural precursor cells in a HA-rich hydrogel in 3D bioprinted constructs, and identified unique molecular dependencies in GSCs, relative to sphere culture [74]. In a 3D-bioprinted mini-brain model, the interaction between GBM cells and GBM-associated macrophages (GAMs) has been recapitulated as an accurate representation of TME, indicating GAMs as the crucial factor regulating the progression and invasiveness of GBM [75]. To mimic the TME of GBM comprising the interaction between cancer cells and blood vessels/fibroblasts, Han et al. reported a bioprinting method for recapitulating the TME with a controllable spheroid size. The printed blood vessels consisted of fibroblasts and endothelial cells in GEL, alginate, and fibrinogen, followed by seeding multicellular tumor spheroids of GBM cells onto the blood vessel layer, indicating the feasibility of TME for drug efficacy *in vitro* [76]. Tang et al. further developed the 3D GBM model into biomimetic tri-regional ones, with tumor regions, acellular ECM regions, and an endothelial region with different regional stiffnesses, providing biophysical evidence for tumor cell behaviors and angiogenic potentials, as well as the application of drug screening with biophysical heterogeneity [77].

To prevent well-bioink interactions and create a compatible HTP screening platform, Maloney et al. used an immersion printing technique to bioprinted tissue organoids in 96-well plates and applied them to GBM for drug screening [78]. Inspiritingly, Hermida et al. developed a novel 3D bioprinting strategy using a multi-nozzle extrusion bioprinter to establish GBM models with GSC, co-printed glioma-associated stromal cells, and microglia, allowing control over the spatial organization of GBM for pre-clinical drug screening and interaction between GBM and TME [79].

To explore the potential utilization of 3D bioprinting, photo-thermal therapy (PTT) was applied in a 3D bioprinted GBM construct, incorporating biomimetic keratin-coated gold nanoparticles (Ker-AuNPs) as a photo-thermal agent. The unique optical and thermal properties of gold nanoparticles render them ideal nanomaterials for photothermal therapy. Gold nanoparticles exhibit a plasmon resonance effect on their surface, which enables efficient absorption and scattering of specific wavelengths of light [80,81]. Their adjustable optical properties allow tuning the absorption peak in the visible to near-infrared (NIR) region [82,83]. Furthermore, gold nanoparticles can effectively convert absorbed light energy into heat energy [84], leading to a localized temperature increase that achieves therapeutic effects in photothermal therapy. Moreover, it exhibits excellent biocompatibility and biological activity [85]. Excitingly, a homogeneous cell distribution of fluorescent-labeled Ker-AuNPs was found, resulting in the extraordinary ability to generate heating at a fast speed [86]. On 3D printed mini-brains, the synergistic therapeutic of photodynamic therapy (PDT) and immune-metabolic modulation effectively recapitulate the biologically relevant interactions between GBM cells and macrophages to elicit a strong immune response and the proliferation of T lymphocytes [87]. Smits et al. successfully verified the potential of a small molecule antagonist of N-cadherin, the cell adhesion molecule for the treatment of GBM in a 3D bioprinting complex mimicking cancerous tissues [88]. The potential utilization of all-trans retinoic acid (ATRA) for targeting GBM cells was evaluated in a 3D bioprinting to fabricate hydrogel meshes laden with ATRA-loaded polymeric particles, which facilitated a sustained release of ATRA with a tunable release rate, inducing apoptotic cell death in GBM [89]. Chadwick et al. even developed a four-dimensional (4D) cell-culture array with thermo-responsive shape memory polymer (SMP), which can self-transform in time when heating, poising to offer rapid assessment of drug responses in PDO from GBM [90].

For benign brain tumors, 3D bioprinting technology also performs as an excellent *in vitro* model. Diao et al. focused on growth-hormone-secreting pituitary adenoma (GHSPA), a benign tumor with high incidence and poor life quality, and used 3D bioprinting to establish a GHSPA microtissue model, which exhibited more active cell cycle progression, secretion, proliferation, invasion, and tumorigenesis than 2D model [91]. The 3D bioprinted GHSPA construct may facilitate the associated investigation in-depth.

1.3.2. Neuroblastoma

In Pediatrics, neuroblastoma (NB) is a common extracranial solid malignancy, leading to early cancer-related deaths in children due to chemotherapy-resistant relapses and resistance to induction therapy [92]. As increased tissue stiffness is one of the characteristics of malignant solid tumors [93], 3D bioprinted hydrogels with different stiffness were applied to investigate the heterogeneity of NB and its cell cluster dynamics and behavior [94,95]. To explore the morphological parameters of 3D spheroid, Duarte et al. fabricated a miniaturized 3D advanced NB model using collagen type I-based bioprintable bioinks. Interestingly, NB cells with bioprintable bioinks formed Homer Wright-like rosettes with proliferation ability and Vimentin-rich matrix, which were successfully bioprinted as compartmentalized 3D models in the centimeter scale and were supposed to attain stable rheological and mechanical properties after bioprinting [96].

Angiogenesis is the hallmark of solid tumors to support the uncontrolled proliferation of tumor cells under hypoxia conditions [97]. Ning et al. applied a GEL methacryloyl (GELMA) bioink to create multi-channel cubic tumor analogs with high printing fidelity and mechanical tunability, filled with NB spheroids and human umbilical vein endothelial cells (HUVECs). Interestingly, the NB-HUVEC integration increased the aggressive behavior of NB as a dynamic culture model [98]. Nothdurfter et al. developed another micro-vascularized tumor-environment model with a GEL-methacrylate/fibrin-based matrix containing multiple cell types to promote the formation of micro-vessel by embedded endothelial cells spontaneously. Based on this model, micro-vessels produced buds into NB spheroids were detected followed by the attraction from the latter one [99].

For anti-cancer drug development, Wu et al. established a 3D bioprinted NB model in a renal environment of exclusively human origin, providing a platform for testing the cytotoxicity and tumor selectivity of new anti-cancer drugs. The open scaffold design in this model guarantees the exchange of the tumor and its microenvironment regardless of cell type, avoiding the limitation of animal models in which human cancer cells are surrounded by an animal-derived environment [100]. Another useful approach against NB with high

morbidity and mortality rate is oncolytic viruses through inducing direct tumor cell death and immune response of anti-tumor. Based on previous findings that M002, and oncolytic herpes simplex virus expressing murine interleukin-12 (mIL-12) targets and kills long-term passage tumor cells, Quinn et al. investigated M002 in 3D bioprinted tumor models derived from NB patients, causing significant tumor cell death [101].

Fortunately, chimeric antigen receptor (CAR) T cell therapy has proved to be an effective treatment strategy targeting NB by clinical trials [102,103]. However, 3D solid tumor architecture may affect the efficacy of CAT-T cells, as less effectiveness was found in mouse models than in 2D cocultures. Grunewald et al. used the 3D bioprinting approach to assess CAR-T cells targeting the L1 cell adhesion molecule, L1CAM and found that L1CAM-specific CAR-T was strongly activated by NB cells in the 3D model, which is highly reproducible, allowing the detection and quantification of CAT-T cell infiltration in tumors [104]. It could be further refined by adding additional cell types representing important tumor components, potentially reducing the time and animals necessary for preclinical testing in CAR-T cell treatment.

1.3.3. Breast cancer (BC)

The incidence of breast cancer (BC) has increased yearly over the past four decades as the leading one in females worldwide [105]. BC-related death is usually due to distant metastasis, most typically occurring in bone [106]. Morre et al. created a 3D bioprinted bone marrow structure with varied methylcellulose/alginate ratios, facilitating the study of BC cell survival in bone marrow [107]. The 3D bioprinted biomimetic bone matrix provided an appropriate structure to investigate the interaction between BC cells and bone stromal cells. In GELMA hydrogel with nanocrystalline hydroxyapatite, cocultured BC cells increased the secretion of VEGF with enhanced proliferation, as a suitable model in the context of an artificial bone microenvironment [108]. Another 3D bioprinted bone construct by Wang et al. was used to evaluate the efficacy of AZD7762, an inhibitor of checkpoint kinase 1/2 (Chk1/2), which significantly suppressed the proliferation of BC cells and the differentiation of pro-osteoclasts [109].

The self-assembles of collagen type I into 3D fibrous networks are the structural basis influencing tissue development, homeostasis, and disease progression. Using 3D microextrusion printing, Nerger et al. developed a new approach to engineer cell-laden networks of aligned collagen type I fibers with controlled alignment and geometry of collagen fibers surrounding cells in the bioink, finding that human BC cells cultured on 3D bioprinted collagen constructs orient along the direction of collagen fiber alignment [110].

In BC, ECM is also involved in tumor progression and drug resistance as a vital factor [111]. Since the development of the method for the bioprinting of cell-laden constructs with novel decellularized ECM (dECM) bioink [112], the dECM-based biomaterials for recapitulating the native tumor-supporting matrix have been developed rapidly [113]. For example, 3D bioprinting of scaffolds containing BC cells and stroma cells with bioink incorporating collagen type I resulted in increased BC cell proliferation and reduced doxorubicin sensitivity [114].

In BC, adipose tissue and adipose-derived mesenchymal stem/stromal cells (ADMSC) are considered the major stromal cells in TME favoring the cancer progression [115]. A 3D bioprinted BC model with BC cells onto adipose tissue constructs revealed the cancer cell-induced reduction of lipid content and the remodeling of ECM within adipose tissues, with increased fibronectin, and collagen I/VI expression [116]. To mimic *in vivo* TME, Wang et al. established a 3D bioprinted construct with central BC cells surrounded with ADMSC using dual hydrogel-based bioinks, which reduced the percentage of cleaved caspase-3 positive cells in response to doxorubicin treatment associated with the thickness of ADMSC [117]. Chaji et al. evaluated multicellular cell-laden hydrogels comprised of adipocytes and BC cells, confirming the feasibility of efficiently fabricating multicellular cell-laden bioprinted models of TME in BC [118]. The coculture of BC cells and fibroblasts in a 3D bioprinting cancer model was also examined to mimic the heterogeneity of native TME, resulting in high viability for long-term cell culture and self-assembly of BC cells into multicellular tumor spheroids [119].

In a 3D-bioprinted avascular structure, Bojin et al. investigated and recapitulated the feature of TME in BC, that is remodeled hydrogel by BC cells, heterotypic aggregates of malignant and peritumoral cells, constituent cell proliferation *in vitro* [120]. For the vascularized model, HUVECs were applied with MDA-MB-231 cells to construct a 3D microenvironment for BC, loaded in human dermal fibroblasts laden fibrin as tumor stroma, impacting the transcriptional profiling involved in tumor angiogenesis and cancer invasion [121]. Thermo-crosslinked sacrificial GEL microspheres encapsulating HUVECs printed by electrospraying as auxiliary component and GELMA precursor solution mixed with subject cells as subject component proposed an innovative bioink system with "secondary bioprinting", promoting the nutrient/oxygen delivery in large-scale tissue and accelerating the functionalization of the encapsulated cells with the successful building of vascularized BC tissues over 1 cm [122]. A bioprinting of cancer cells onto excised mouse tissues, as a native microvasculature model, enabled real-time tracking of cellular proliferation and migration within a physiologically relevant microenvironment. Importantly, not only cancer cell clusters were colocalized with angiogenic microvessels, but also vascular islands were increased for tissues with bioprinted cancer cells, indicating the influence on angiogenesis by the presence of cancer cells [123].

BC spheroids grown to 10 days in concave structures exhibit hypoxic cores and necrosis, while 3D bioprinting based on cellular spheroid structures using MCF-7 cell-laden alginate/GEL hydrogel facilitated the long-term 3D cell culture. PDT-induced death of tumor spheroids showed a random distribution in hydrogel, which mimics ECM, enabling integrative in situ measurement of tumor spheroid by laser [124]. To detect real-time information on cell metabolism, Dornhof et al. bioprinted tumor spheroids directly into microwells of a chip-based electrochemical oxygen sensor array, allowing single MCF-7 spheroids close to the sensor electrodes and detecting cellular respiration rates and the alteration of cell metabolism when exposure to drugs [125]. To precisely control both spatial patterning and size of cell-encapsulating microbeads, Kingsley et al. reported laser direct-write (LDW) on a 3D bioprinting technique for precise fabrication and placement of alginate microbeads, as a versatile biomanufacturing platform for bioprinting to generate size-controlled 3D multicellular aggregates, such as BC cells and embryonic stem cells [126,127].

For small molecule screening, Engel et al. demonstrated a 3D cell culture platform through an HTP bioprinter RASTRUM and an

HTP screening assay AlphaLISA. With the results of doxorubicin treatment on BC cells, the workflow offers an efficient, cost-effective, and compatible alternative to the traditional 2D one [128]. Even for drug-resistant BC spheroids, 3D bioprinting hydrogel enabled the quantitative determination of anti-cancer efficacy [129]. Han et al. used a 3D bioprinting technique to mimic the clinical stage of cancer in individual patients with different levels of high hypoxia, mesenchymal marker expression, and invasion activity, providing a physiologically relevant BC model for personalized medicine *in vitro* [130]. Drug delivery is also an important factor affecting anti-cancer efficacy. Using a 3D bioprinted BC model, it is found that decreased pH value by omeprazole and lansoprazole effectively enhanced the transportation of doxorubicin into spheroids [131–133]. Genetically engineered T cells targeting BC cells effectively eliminated tumors in the 3D bioprinting model, by recognizing major histocompatibility complex class I-related protein expressed by tumor cells in the presence of precursor MAIT cell ligand 5-amino-6-D-ribitylaminouracil [134].

Compared with conventional BC spheroids, 3D bioprinted ones were significantly suppressed by PTT using MXenes through increased reactive oxygen species level, possibly due to the presence of ECM enhancing thermal conduction [135]. Nam et al. used AuNPs to improve the treatment as plasmonic PTT by generating destructive heat upon irradiation in bioprinted 3D complex tissue constructs [136]. To extend the utilization of 3D bioprinting technology, Reid et al. designed a low-cost bioprinting platform for evaluating tumorigenesis and TME-redirection of BC cells, which significantly increased tumoroid formation in 3D collagen gels and mimicked co-printing cancer cells along with normal epithelial cells for chimeric organoids [137]. The paper-based device was another matrix-assisted sacrificial 3D bioprinting, possessing unique properties including its natural origin, good biocompatibility, and low cost, providing new strategies for constructing simple and low-cost *in vitro* tissue models [138].

1.3.4. Epithelial ovarian cancer (EOC)

Epidemiology shows that epithelial ovarian cancer (EOC) is the leading cause of death from female gynecologic malignancies, accounting for 4% of all cancers in women [139]. The study of the EOC genome suggested the heterogeneity of ovarian cancers, providing the theoretical basis for the design of 3D biological printing cancer models, which is conducive to early and accurate predictive EOC and specifying precise diagnosis and treatment plans [140].

In a 3D bioprinted EOC model with cancer cells and cancer-associated fibroblasts (CAFs), cancer cells self-assembled in heterotypic aggregates by recruiting CAFs surrounding cancer cells in a process similar to the *in vivo* process [141]. Endothelial cells were also used to co-culture with EOC spheroids in another 3D bioprinting system to investigate the function of MDM4, a well-known p53-inhibitor in EOC, showing reduced dissemination and intravasation of MDM4-expressing EOC cells through mTOR signaling pathway [142]. Surendran et al. engineered a novel microfluidics-integrated 3D Chip device based on tumor-immune microenvironment (TIME). Tumor spheroids on hydrogel-based multi-microwell pates within collagen matrix of certain thickness were magnetically hybrid-integrated with a 3D bioprinting enabled microfluidic system carrying neutrophils. Interestingly, in this Chip device, neutrophils generated neutrophil extracellular traps (NETs) in response to the growing tumor spheroids, which in turn stimulated the reciprocation of tumor cells from aggregated state to collectively invade into the surroundings, suggesting the important role of NETs in the induction of collective invasion of EOC cells [143].

For HTP purposes, Xu et al. built a multicellular acini on an EOC cell overlaid on Matrigel™ 3D model, as an HTP automated cell printing system to bioprint a 3D coculture model using EOC cells and normal fibroblasts micropatterned on Matrigel™ in a reproducible manner. This 3D bioprinting model enables the miniaturization of a macro-scale 3D culture model, allowing systematic investigation into multiple unknown feedback and/or interactions between tumor and TME in an HTP manner [144].

1.3.5. Skin tumor

Cutaneous melanoma is a kind of malignancy with a very poor prognosis mainly due to metastatic dissemination [145], while cutaneous squamous cell carcinoma (cSCC) is the most deadly form of non-melanoma skin cancer [146]. Although traditional 2D cell culture reflects the characteristics of cancer to a certain extent, how to reveal complex pathophysiological conditions is still a challenge [147]. 3D bioprinting is a promising technique, used to create artificial skin constructs in a collagen matrix with micro-channels for adequate vascularization [148].

For skin cancer investigation, 3D bioprinting is also adapted to mimic the tumor's physiological environment. In different cell models, including skin epithelium (HaCaT), skin cancer (A431), liver cancer (HepG2), and fibroblasts (3T3-J2), Jeffries et al. optimized the bioprinting technology and proposed a novel microfluidic method, capable to position individual cell in complex 2D and 3D pattern as well as single-cell arrays. Only 20–35 μl of cell suspension allowed the construction of small tissues with excellent viability and survival, which can minimize the loss caused by handling and transferring cells when working with scarce and valuable samples [149].

To screen novel, effective, and less toxic small molecules targeting cSCC, especially on metastatic and locally advanced ones, Browning et al. constructed a morphologically and physiologically accurate 3D bioprinted skin model of cSCC cells with a fluorescence confocal imaging assay. The efficacy and general toxicity of chemotherapeutics were detected based on tdtomato-labeled cSCC cells and ZsGreen-labeled keratinocytes, indicating that half of the cancer cells were killed in this model with 1 μM 5-Fluorouracil treatment and normal keratinocytes were less affected during this treatment. This platform supports cellular-level measurement of cell viability and achieves non-destructive HTP screening in biofabricated tissues [150].

As malignant melanoma is usually applied as the model tumor for evaluation of novel therapies, Schmidt et al. bioprinted fluorescently labeled melanoma cell lines with Matrigel and commercially available bioinks, with or without modification to increase cell-matrix communication. GELMA-based bioink promoted cell proliferation in clusters, while no proliferation was found at all in alginate-based bioink, providing precisely adapting extracellular matrices to individual requirements in specific 3D bioprinting [151].

1.3.6. Colorectal cancer (CRC)

Colorectal cancer (CRC) ranks third in incidence (6.1%) but second in mortality (9.2%), with an estimated 60% and 71.5% increase in deaths by 2035, from rectal and colon cancer, respectively [152]. A hybrid nanoink composed of alginate, GELMA, and cellulose nanocrystal (CNC) was designed for multi-nozzle microextrusion 3D bioprinting CRC models with the ratio of 2:4:6, successfully constructing a 3D bioprinting of a CRC model coupled with dual ultraviolet and ionic cross-linking [153].

The post-viability was successfully monitored at least for 7 days in bioprinted 3D human colon cancer cell constructs, which were integrated into a 3D-bioprinted perfused drug screening microfluidics platform [154]. To improve preclinical disease models for individualized therapies, an affordable, flexible, and highly reproducible 3D bioprinted CRC model was established, and RNA expression profiles in 3D bioprinted cells showed significantly increased expression of genes involved in cell adhesion, hypoxia, EGFR/KRAS signaling, while decreased cell cycle program [155]. To mimic *in vivo* cell physiological function, Chen et al. cocultured CRC cells, CAFs, and tumor-associated endothelial cells (TECs) on 3D-printed scaffolds to constitute an ECM of tumor tissues, which exhibited physiological activity drug resistance similar to that observed in tumors in *vivo* [156]. An acoustic bioprinting technology was used to encapsulate CAFs derived from CRC patients into gel droplets and print them into a 3D CAF microtissue construct, which can monitor the cancer cell migration and invasion from the tumor organoid derived from the same patient to the 3D CAF construct and investigate cancer invasion dynamics and therapeutic response with time-lapse imaging [157].

Polyamidoamine (PAMAM) dendrimer was applied for efficient delivery of siRNA to tumor cells but with the associated toxicity problems rendering its use in biological applications [158]. To address this problem, lipodendriplexes, a non-covalent lipid modification, were applied to construct an effective knockdown system with siMDR1, which significantly reduced the tumor cell migration in 2D and 3D cell cultures through downregulating the MDR1 gene effectively [159]. Another investigation proposed the nanoclay to increase the printability and constructed a 3D bioprinting CRC model with GELMA-nanoclay hybrid hydrogels, which induced and enriched CRC stem cells with elevated levels of stemness markers [160].

1.3.7. Liver cancer

Hepatocellular carcinoma (HCC) is a kind of malignancy associated with liver fibrosis and cirrhosis, with high morbidity and mortality rates worldwide [161]. The increased stiffness of the ECM due to liver fibrosis or cirrhosis has a significant impact on the development and progression of HCC [162]. Therefore, simulating the 3D mechanical environment in primary liver cancers is important to study the biomechanical mechanisms of HCC. The automated fabrication of a cell-dense, thick human vascularized liver tissue models involved in 3D bioprinting and incorporation of primary human hepatocytes, non-parenchymal cells, and isolated fragments of intact human microvessels as vascular precursors, were served as a useful platform for a variety of applications in liver disease modeling, infectious agent studies and cancer investigation [163].

3D printing, co-culture, and microfluidics are important methods to construct *in vitro* drug models with a high degree of bionics. To take the combined advantages of these three methods, Li et al. constructed a 3D co-culture microfluidic model with controllable hepatoma cluster size. The hepatoma cells proliferated faster than common *in vitro* 3D models fabricated by cell printing only and were less affected by the increased drug concentration in migration performance [164]. Xie et al. constructed hepatorganoids with HepaRG cells retaining liver function and extended to establish an individualized HCC model derived from patients after surgery, which grew well during long-term culture and retained the features of parental HCC, capable of displaying the results of drug screening individually [165].

For malignancies in the biliary system, 3D bioprinting also showed its potential utilization in treatment. Mao et al. bioprinted a personalized *in vitro* model with intrahepatic cholangiocarcinoma (ICC) into a 3D construct using a composite hydrogel system of GEL/alginate/Matrigel™. The researcher also evaluated this in a 3D bioprinting model and successfully obtained the anti-cancer drug resistance demonstrating stem-like properties [166]. To explore the effects of stromal cells on cholangiocarcinoma (CCA), Li et al. applied the 3D bioprinting model with both tumor cells and stromal cells, which exhibited better proliferation, high tumor-related gene expression and chemoresistance promoted by the existence of stromal cells [167]. At the same time, silk fibroin-GEL/HA/heparan sulfate (SF-GHHs) scaffolds with 350 ± 102 μm pore size were proved to harbor optimal porosity, good water uptake, and stable beta-sheet, supporting the proliferation and aggression of CCA cells with increased CCA stem cells and EMT markers [168].

1.3.8. Pancreatic cancer

3D bioprinting is being applied to create tumor models for pancreatic adenocarcinoma, the second most lethal cancer worldwide [169]. Magnetic 3D bioprinting (M3DB) was used to emulate cell-TME interaction with high resistance to toxic agents, while Stable Isotope-Resolved Metabolomics (SIRM) with $13C_6$-glucose tracer was employed to map central metabolic network in 2D cells and M3DB spheroids formed from lung and pancreatic adenocarcinoma cells, revealing the changed mentalism and potential mechanism of increased resistance [170]. And 3D bioprinting serving as models for fast and affordable HTP screening in diverse malignancies, including pancreatic cancers, showed the potential for faster identification of promising compounds for cancer treatment [171]. Hou et al. ameliorated the 3D bioprinting models by combining a cell-repellent surface with a bioprinting technology incorporating magnetic force, to establish an HTP screening-compatible method enabling the consistent production of organoids in standard flat-bottom plates. Based on the PDC of pancreatic cancer, appropriate 3000 drugs were evaluated for their cytotoxicity in this model, which is proved to be ready for large-scale drug screening [172].

To improve the mechanical integrity of a hydrogel material, Habib et al. developed SA with carboxymethyl cellulose as a novel hybrid hydrogel with validated printability, shape fidelity, and cell viability, and optimized for 3D scaffold pancreatic cancer cell structures with 86% cell viability after 23 days [173]. In the investigation of pancreatic ductal adenocarcinoma (PDAC), laser-assisted

bioprinting was used to generate 3D pancreatic cancer spheroids arrays, providing a suitable model for exploring the internal/external factors associated with the formation of precursor PDAC lesions and cancer progression [174].

As TME is also an important factor interacting with pancreatic cancer, multiple cell types cocultured in defined architecture as 3D bioprinted constructs altered cellular proliferation, ECM deposition, and cellular migration in response to extrinsic signals or therapies [175]. Noel et al. developed a rapid generation method of 3D spheroids co-cultured pancreatic cancer cells and activated pancreatic fibroblasts, through an extracellular flux analyzer paired with a spheroid microplate [176]. Human dermal fibroblast cells can also be co-cultured with pancreatic ductal adenocarcinoma in 3D bioprinting cell culture models for evaluating a versatile ink comprising a 4-arm poly(ethylene glycol)-based polymer with distal maleimide derivatives to form the hydrogel in less than a second [177]. Meanwhile, Xu et al. reported surface-engineered biomimetic inks based on cellulose nanofibrils (CNF) and cross-linkable hemicellulose derivatives for UV-aided extrusion printing, demonstrating great cytocompatibility and supported ECM adhesion and proliferative behaviors in cocultured human dermal fibroblasts and pancreatic tumor cells [178].

1.3.9. Lung cancer

Lung cancer frequently occurs worldwide, and its annual incidence is increasing along with the effects of increased environmental pollution and smoking, and the disease has now become the focus of clinical treatment, including radiotherapy as the main method [179]. In a 3D bioprinted lung cancer model, Al-Zeer et al. evaluated the suitability of standardized samples in radiotherapy. Surprisingly, the 3D printed constructs were sufficiently mechanically stable with peak doses up to 400 Gy for cytotoxicity testing [180].

The development of stable and ready-to-use bioinks based on the xeno-free and tunable hydrogel system has allowed for the creation of cell-laden scaffolds for extrusion bioprinting without UV curing or temperature adjustment. The optimized polysaccharide-based ink, H4-RGD showed excellent printability between 20 and 37 °C, inducing rapid spheroid growth of non-small-cell lung cancer (NSCLC), and TME formation within 7 days [181]. To develop a GEL-SA hydrogel used to print NSCLC patient-derived xenograft cells and lung CAF co-cultures using 3D bioprinting technology, the hydrogel was optimized to enhance printability and cell viability, resulting in the formation of co-culture spheroids within the printed scaffold [182]. A new methodology for scaffold-free 3D cell culture and cellular assembly via magnetic levitation in the presence of paramagnetic agents has been developed to evaluate the formation of complex 3D cellular structures without compromising cell viability [58]. In the fabrication of a cell-laden hydrogel grid scaffold structure, GEL-SA-lung cancer cell A549/95-D suspension was examined as the bioink, indicating enhanced invasion and migration capabilities [183].

1.3.10. Challenges facing 3D bioprinting for anti-cancer applications

As mentioned above, 3D bioprinting has been emerging as a promising technology with the potential to revolutionize anti-tumor applications (Table 1). It aims to print 3D tissue constructs using biomaterials to replicate a more accurate mimic of *in vivo* solid tumors with interaction between cancer cells and their TME surroundings, potentially improving drug delivery and screening drug responses.

It is important to maintain the viability and function of cells in 3D bioprinting models for further investigation. However, due to

Table 1
The application of 3D bioprinting in anti-cancer aspects.

Malignancies	Printing type	Cancer models	Purposes	References
Glioblastoma	Laser printing	Reproducible and scalable Glioblastoma tissue models with stromal materials, tumor and non-tumor cells	To investigate drug sensitivity, cellular interactions, and immune response in a neural environment	[74]
Neuroblastoma	Inkjet printing	In vitro vascular model in combination with neuroblastoma spheres	To create a platform for high-throughput investigation studies that scrutinize the complex cellular molecular mechanisms of tumor microenvironment in growth, invasion, and response to therapies	[98]
Breast cancer	Inkjet printing	Cancer cells aggregated with microstructures resembling breast cancer histomorphology, including ductal and solid patterns	To mimic the morphological heterogeneity and cellular attributes of natural cancer tissues, and enhance personalized medicine applications	[130]
Ovarian cancer	Laser printing	A micro-fluidically integrated microarray device to simulate the 3D tumor immune microenvironment	To investigate the mechanism that neutrophils initiate collective 3D invasion of cancer cells and explore the impact of chemotaxis and neutrophil extracellular trap formation on the behavior of cancer cells	[143]
Melanoma	Inkjet printing	A trilaminar model of malignant melanoma consisting of multiple cell types	To replicate the tumor microenvironment and aid vascularization for individualized treatment	[150]
Colorectal Cancer	Inkjet printing	A 3D bioprinting cancer model with induced and enriched cancer stem cells	To investigate heightened stemness, sensitivity, and potential therapeutic options	[160]
Hepatocellular carcinoma	Inkjet printing	An individualized 3D bioprinted model of hepatocellular carcinoma (3DP-HCC)	To yield intuitive drug-screening results and aid personalized treatment	[165]
Pancreatic cancer	Laser printing	The bioinks and printed scaffolds with the ability to promote biocompatibility	To construct adjustable hydrogel scaffolds with varied mechanical properties for tissue engineering, cellular research, and drug screening	[178]
Non-small-cell lung cancer	Inkjet printing	A 3D bioprinting lung cancer model with patient-derived xenograft cells co-cultured with lung cancer-associated fibroblasts	To optimize the rheology of SA-GEL hydrogels and generate 3D co-culture spheroids for drug screening and preclinical utilization	[182]

increased temperature, pressure, and chemicals, cells may lose their function, and even die during the printing process [184]. Therefore, further research could focus on verifying the optimal conditions to protect the cells for survival and normal function, including the viscosity and extrusion rate of the bioink, as well as the nozzle movement speed. Another issue that should be addressed is cell differentiation and directed differentiation in the 3D bioprinting process. Unfortunately, current technologies have not investigated such a field, which may be the reason leading to the failure of tissue engineering constructs.

As 3D bioprinted tissues are the main result of the 3D bioprinting process, how to evaluate their quality is still a major challenge. To explore the biomedical application of different bioinks, Rastin et al. examined the potential of MXene cell-laden bioinks for tissue engineering and found their ability to assemble functional scaffolds to regenerate damaged tissue through 3D bioprinting, suggesting the potential utilization of MXene nanocomposite bioinks and their 3D bioprinting with high electrical conductivity, biocompatibility and degradability [185]. However, depositing different cells at the desired location is not easily achieved due to poor cell adhesion [186].

Improving the precision and resolution of 3D printing technologies is also critical for the fabrication of biological tissues and organs with complex structures. However, current 3D bioprinting technologies still have such limitations. For example, patterned microcapillaries are still difficult to achieve [187], and precise spatial placement and alignment of many key components remain challenges for 3D printing [42], while improved precision will facilitate the study of interaction mechanisms in elements of TME [188]. Nowadays, almost all 3D bioprinting technologies are unable to build complex tissue structures such as blood vessels and neural networks [189]. Although some studies have initially simulated the open channel network of the vascular system through bioprinting of sacrificial materials [187], the construction of complex structures with stable vascularized and non-vascularized regions is needed to develop pro-angiogenic and anti-angiogenic bioinks containing endothelial cells [190]. The mismatch between the natural tissue

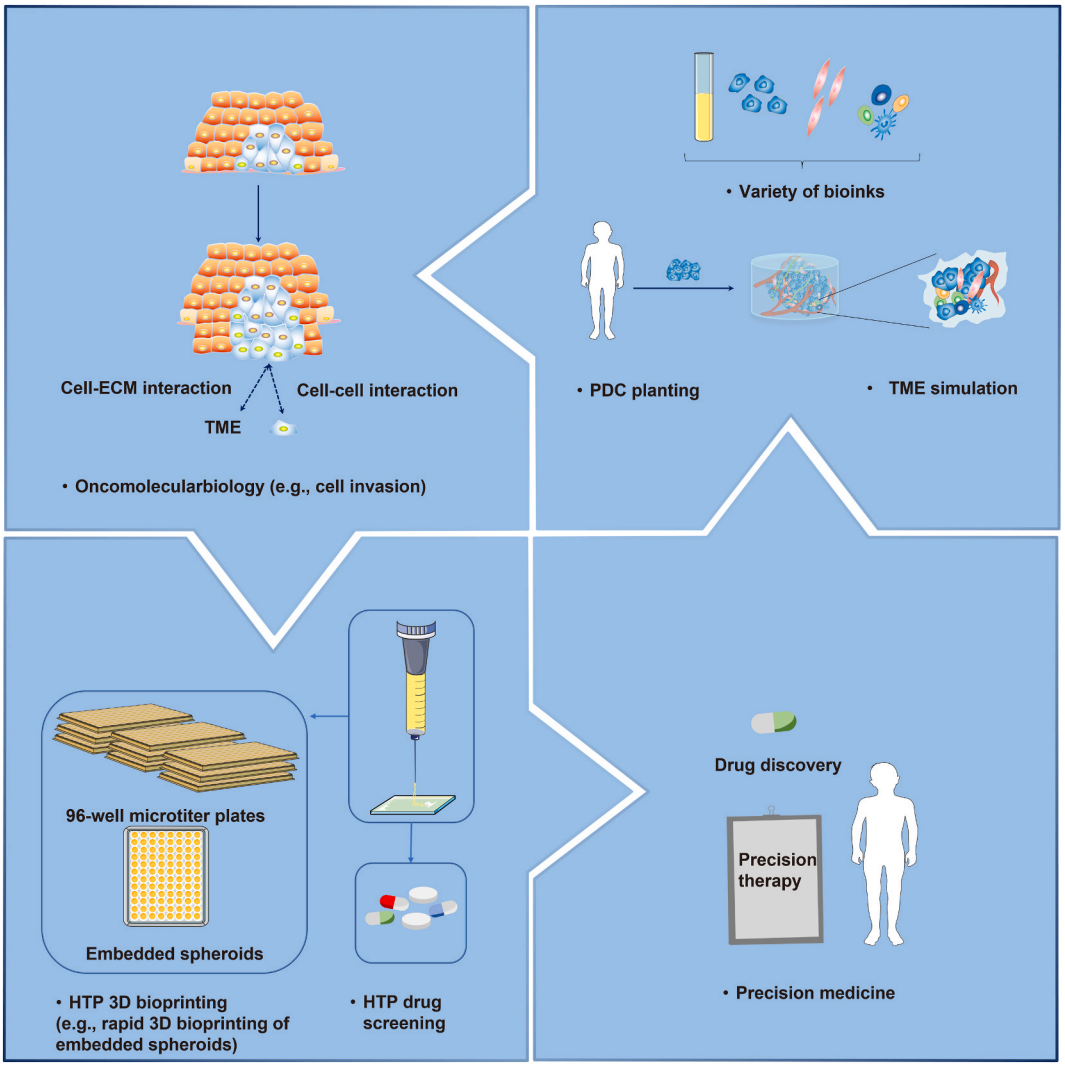

Fig. 3. The application of 3D bioprinting in anti-cancer aspects. ECM: extracellular matrix; PDC: patient-derived cells; HTP: high-throughput.

environment and the properties of the designed bioinks remains a challenging aspect [191], with limited bioprinting materials currently available, mainly cells and biopolymers [192].

The selection and properties of these materials are also limited by the lack of mechanical properties and degradability of natural biopolymers [193] and the clogging of printing systems by bioinks with high-viscosity solution collagen ECM [194], so further research is needed to develop new materials that combine mechanical properties and biocompatibility with stable cross-linking strategies to create stable scaffold [195].

Calcium concentration can also affect cell viability, while low viscosity inks also mean reduced printing resolution, which remains a big challenge to address [196]. Currently, the supply chain of biopolymers and cells is fragmented and fragile, which may affect the development of 3D bioprinting technology. Imaging techniques, optical analysis and chemical evaluation methods for 3D structures, and tumor preparation processes need to be further refined and equipped [197]. The speed and scale of 3D bioprinting also should be improved with further investigation [198], and current 3D bioprinting technologies cannot meet the requirements of high precision and high speed. More time is needed to fabricate biological tissues and organs with complex structures.

Cost should not be negligible, mainly due to the high cost of bioprinting materials, devices, and technologies. Therefore, cheaper and more efficient bioprinting technologies need to be researched to facilitate the development of this technology. With further research and development, 3D bioprinting has the potential to revolutionize antitumor applications and provide personalized treatments for a range of cancer types.

2. Conclusion

3D bioprinting technology exhibits promising potential for constructing diverse functional tissue models, encompassing a wide range of applications including anti-tumor research (Fig. 3). In this domain, 3D bioprinting can be employed to simulate the TME, which plays a pivotal role in tumor initiation, progression, and metastasis. By precisely regulating cell-cell interaction, cell-ECM interaction, and the architecture of vascular networks, 3D bioprinting offers a more realistic and dynamic platform for investigating the interplay between tumor cells and their surroundings. Moreover, the introduction of HTP-3D bioprinting manufacturing platforms has further propelled research progress by enabling the rapid construction of numerous complex tissue models. Consequently, HTP drug screening can also be conducted more efficiently to evaluate drug efficacy within these models.

However, the current state of 3D bioprinting technology presents several challenges and limitations. A primary obstacle is achieving the precise printing of intricate tissues. While notable progress has been made in arranging cellular and extracellular matrix components spatially, there remain difficulties in accurately replicating the intricate and authentic tumor microenvironment. Furthermore, the selection of suitable biological inks, enhancement of cell viability, and the creation of functional tissues require further exploration and resolution.

As manufacturing techniques advance and materials science continues to evolve, it is reasonable to anticipate the emergence of more sophisticated and lifelike tumor models. Additionally, 3D bioprinting holds the potential to construct personalized tumor models utilizing PDCs and bioinks. This advancement will drive further progress in precision medicine and immunotherapy. In this context, cancer models produced through 3D bioprinting are poised to expedite the identification of therapeutic targets, diminish reliance on animal testing, and potentially mitigate the global cost burden of cancer treatment. The incorporation of HTP-3D bioprinting and HTP drug screening will further invigorate this process, expediting innovation in both medical research and treatment strategies.

Author contribution statement

All authors listed have significantly contributed to the development.

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Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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