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REVIEW ARTICLE

Bioprinting in tumor model construction for head and neck squamous cell carcinoma: A review

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is a malignancy with increasing incidence worldwide, causing a severe impact on the quality of life and survival rate of affected patients. Traditional tumor models have significant limitations in studying biological properties, tumor microenvironment, and treatment response, and the difficulty in obtaining HNSCC specimens has hampered our understanding and the development of treatment for the disease. Recent rapid development in bioprinting has provided new possibilities for tumor model construction, enabling precise control of cell arrangement and tissue structure to be more realistically simulated tumor biological properties. This review summarizes the latest progress of bioprinting in HNSCC tumor model construction, explores the application of different bioprinting technologies, the properties of constructed tumor models, and the potential applications of these models in drug screening and individualized treatment, aiming to provide reference and inspiration for future research and treatment of HNSCC.

Keywords: 3D microenvironment; Bioprinting; Head and neck squamous cell carcinoma; Tumor model construction

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1. Introduction

Epidemiological data indicate that the incidence of head and neck squamous cell carcinoma (HNSCC), a prevalent and highly aggressive malignancy, is rising globally. In 2020, there were about 900,000 new cancer cases and around 500,000 deaths all over the world.[1] Despite advancements in early diagnosis and treatment in recent years, the high recurrence rate and metastatic potential of HNSCC continue to pose significant challenges in clinical management; therefore, developing new agents for affected patients and conducting drug efficacy assessment are desperately needed.[2]

In oncological research and treatment, conventional tumor models (such as mouse subcutaneous tumor models and cell line models) have been widely used in drug development and efficacy evaluation. They are advantageous due to their ease of establishment and maintenance, allowing researchers to obtain experimental results within a relatively short timeframe[3] and at a lower cost compared to more complex models.[4] However, conventional tumor models exhibit substantial limitations in accurately simulating the tumor microenvironment and tumor heterogeneity. These models frequently fall short in replicating the intricate interactions between tumor cells and the surrounding stroma, immune cells, and vasculature, which can result in biased outcomes in drug development and the assessment of therapeutic strategies.[5] Consequently, there is an urgent need to develop innovative tumor models that more accurately represent the biological characteristics and microenvironment of HNSCC.

In recent years, researchers have begun to explore more advanced model systems, such as patient-derived tumor xenograft models (PDX) and genetically engineered mouse models (GEMMs), which can better simulate the biology and microenvironment of human tumors.[6,7] However, these models come with several limitations that can impact their effectiveness in translating findings to clinical settings. Firstly, many traditional xenograft models are developed from immunocompromised mice, failing to represent tumor–immune interactions in humans, leading to potentially misleading immunotherapy efficacy results.[8,9] Secondly, HNSCC is characterized by a diverse range of genetic and phenotypic variations, which can result in inconsistent responses to treatment across different PDX models.[10,11] Additionally, the time required to develop and propagate these models, the engraftment success and growth rates, the anatomical and physiological differences between human tumors and animal models can be limiting factors in the rapid evaluation of new therapies.

Despite the important historical status and practical value of the aforementioned tumor models in cancer research, their limitations also prompted researchers to explore more complex and physiologically relevant models, such as three-dimensional (3D) tumor models and organ chip models, to improve the success rate of drug development and the effectiveness of clinical transformation.[12] The researchers have developed many different types of 3D cancer models using spheroids organoids, biomaterial scaffolds, and cancer chip systems, as summarized in Table 1. The tumor model established by spheroids organoids is currently the most common type of 3D model; however, the successful establishment of the tumor model is dictated by cell–cell interactions at a greater extent but less so by the tumor microenvironment, and controlling the tumor model's size presents difficulty.[13–15] Besides, almost all of these models fail to accurately control the organization of multiple cell types in complex architectures. Bioprinted cancer models can integrate

Table 1. Comparison of existing HNSCC models

Model type	Advantages	Limitations
Bioprinted tumor models	• Precise placement of multiple cell types • Complex 3D architectures mimicking tumor microenvironment • Customizable for specific research needs • Rapid production • Facilitates study of cell–cell and cell–matrix interactions	• Complexity in the bioprinting process • May require specialized equipment
Spheroid models	• Mimics some aspects of tumor architecture and behavior • Useful in studying cell behavior and drug resistance	• Lacks complexity of tumor microenvironment (e.g., stromal cells, ECM) • Limited predictive power for clinical outcomes
Patient-derived explants	• Maintains original tumor architecture and microenvironment • Accurate representation of tumor biology • Valuable for studying patient-specific therapy responses	• Challenging to culture • Less suitable for high-throughput screening • Variability between patient samples complicates data interpretation
Tumor organ-on-chip systems	• Simulates physiological conditions of human organs • Allows real-time monitoring of cellular responses • High control over experimental conditions	• More complex fabrication processes • Limited cell types can be used
3D Co-culture models	• Simultaneous culture of different cell types • Effectively mimics tumor microenvironment • Provides insights into various cell roles in tumor progression	• May lack spatial control and complexity compared to bioprinted models

Abbreviations: ECM, extracellular matrix; HNSCC, head and neck squamous cell carcinoma.

stromal cells and cancer cells into 3D structures to generate tailored models of this complex disease. 3D bioprinting can generate complex, multicellular, and reproducible structures in which the matrix composition and stiffness are tailored to the tumor locally.

The advancement of bioprinting technology presents novel opportunities for tumor research. Bioprinting is an emerging technology designed to achieve the goals of tissue engineering and regenerative medicine by precisely printing biomaterials and cells into 3D structures, as illustrated in Figure 1. The principle is similar to those of conventional 3D printing techniques, but bioprinting places special emphasis on biocompatibility and cellular activity.[16,17] Computer software is used to convert the 3D model of the organ or tissue into computer-aided design (CAD) file digitally. By governing the applicator or needle-syringe in the 3D bioprinter, biomaterials are then printed layer by layer with precision over geometry according to the relevant CAD file. All biomaterials maintain their shape and are as stable as possible during the crosslinking or curing process.[18] The choice of bioink is of paramount importance and generally necessitates the integration of biomaterials (such as hydrogels) and cells to ensure that the printed structures exhibit optimal biocompatibility and functionality.[19] Furthermore, bioprinting must take into account the survival rate and functionality of the cells to ensure that the printed cells can proliferate and differentiate normally within the new environment.[20] With the advancement of these technologies, bioprinting is anticipated to play a significant role in the fields of regenerative medicine, drug screening, and disease modeling.[21]

A comprehensive review of the principles, characteristics, applications, and future trends of the HNSCC model in bioprinting technology is currently lacking. Regarding the establishment of robust preclinical models for investigating the mechanisms underlying HNSCC treatment resistance and progression, as well as refining treatment strategies, to the best of our knowledge, this article presents the first review of the HNSCC model in bioprinting technology.

The remainder of this article is organized as follows: Section 2 provides an overview of bioprinting technology. Section 3 discusses the construction of bioprinting-based tumor models and the selection of materials for HNSCC, summarizing and comparing existing tumor model construction methods and material choices. Section 4

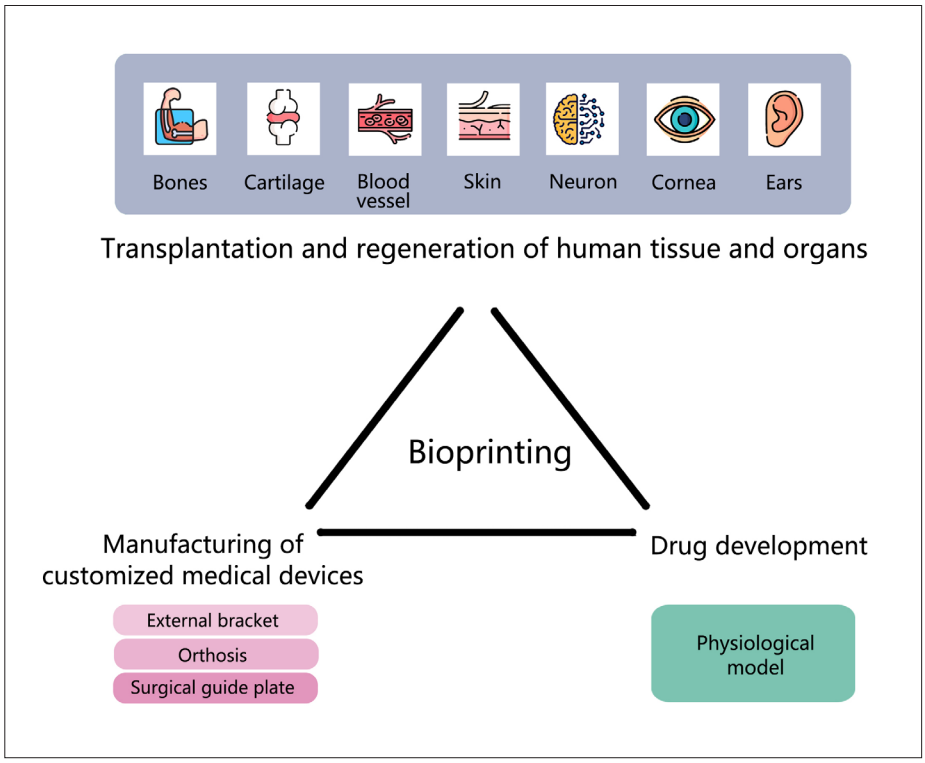

Figure 1. Numerous clinical applications of 3D bioprinting technology, including drug development, tissue regeneration engineering, individualized medical treatment, and precision medical care.

elaborates on the tissue structure and microenvironment reconstruction for the HNSCC tumor model. Section 5 outlines their applications, proposes application guidelines, and highlights key insights. Finally, section 6 lists challenges and offers recommendations for the future development of bioprinting in HNSCC research.

2. Overview of bioprinting technology

2.1. Application of 3D bioprinting in tumor model

3D bioprinting has emerged as a revolutionary technology in the field of cancer research, offering innovative solutions for creating tumor models that closely mimic the *in vivo* tumor microenvironment. Traditional two-dimensional (2D) cell culture methods have significant limitations in replicating the complex interactions between cancer cells and their surrounding microenvironment. In contrast, 3D bioprinting allows for the precise deposition of living cells, biomaterials, and biochemical cues, enabling the fabrication of highly biomimetic tumor models.[22–24] One of the key advantages of 3D bioprinting is its ability to recreate the spatial and structural complexity of tumors. For instance, researchers have successfully developed 3D-bioprinted vascularized tumor models that mimic critical processes such as invasion and angiogenesis. These models facilitate the study of tumor progression and the efficacy of anticancer therapies in a more physiologically relevant context.[22,25] In addition, by utilizing patient-derived cells and biomaterials, researchers can create customized tumor models that reflect the unique characteristics of an individual's cancer. This approach enables high-throughput drug screening and the evaluation of therapeutic responses, ultimately paving the way for tailored treatment strategies.[26,27] Furthermore, the integration of 3D-bioprinted tumor models with computational flow models has been explored to study the dynamics of circulating tumor cells within the vasculature, providing valuable insights into metastasis.[25,28]

2.2. Current mainstream bioprinting technologies

Bioprinting involves the layer-by-layer deposition of biological materials, such as cells, hydrogels, and bioinks, to fabricate 3D tissue constructs.[29,30] Currently, bioprinting technology is primarily categorized into three types, as shown in Figure 2, with inkjet printing and extrusion printing being the most prevalent methods. Inkjet printing employs a nozzle to spray bioink as minute droplets onto a substrate, thereby forming a cellular layer. This technique is advantageous due to its high resolution and rapid printing speed, offering a unique advantage in replicating intricate tumor microenvironments. However, it requires stringent

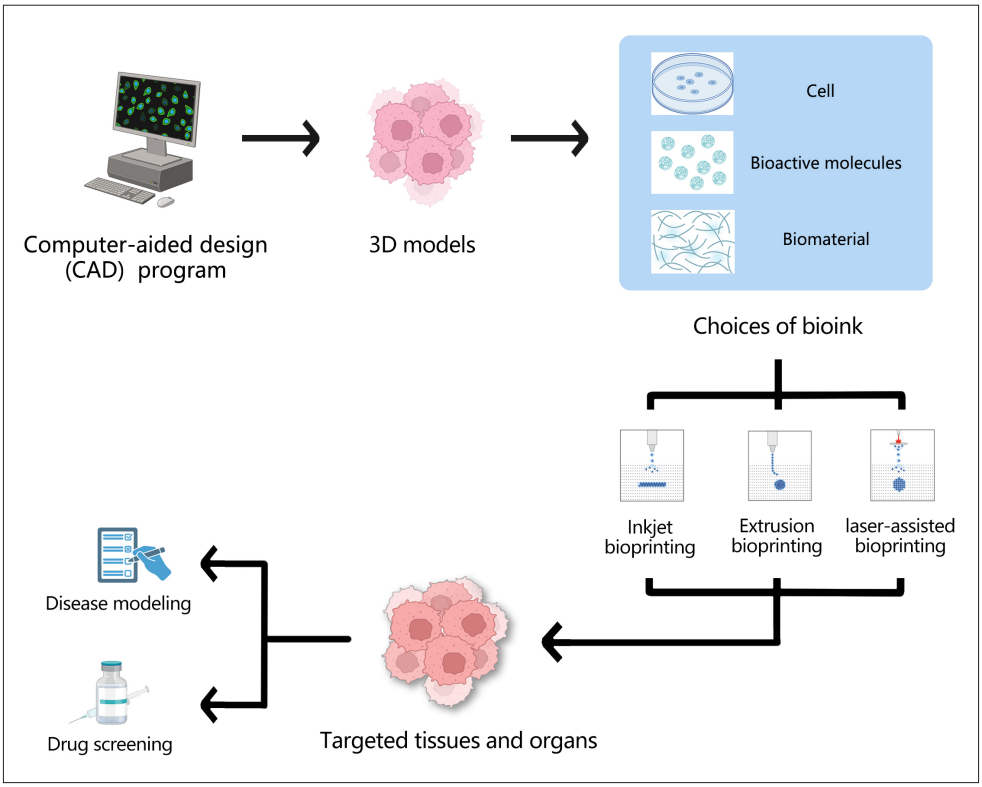

Figure 2. Bioprinting process of the tumor model: computer-aided designing, bioinks selection, and bioprinting.

conditions regarding the viscosity and cell density of the bioink.[31]

In contrast, extrusion printing technology operates by continuously extruding bioinks through an extruder, enabling the fabrication of larger structures that are well-suited for constructing complex tissue and organ models. The versatility of extrusion printing supports a diverse array of biomaterials, including cells, tissue constructs, and microfluidic devices.[32,33] This method excels in controlling printing speed and ensuring effective interlayer adhesion; however, its relatively low resolution may limit its applicability in certain contexts.[33] Extrusion printing is particularly beneficial for the fabrication of large-scale tumor models, especially in applications requiring enhanced mechanical strength.[32,34,35]

Emerging technologies, such as light-curing printing and laser-assisted biological printing, are garnering increasing attention. Laser-assisted printing employs a laser beam to accurately deposit biological materials at specified locations, promoting efficient cellular organization, and the formation of tissue structures critical for replicating the complex architecture of tumor tissues.[36,37] Ultimately, a suitable bioprinting technology is selected based on specific application requirements (see Table 2), such as the desired structural complexity, cell type, and mechanical properties of the target tissue. As technological advancements continue, novel hybrid printing methods that integrate the advantages of existing approaches are expected to further advance research and applications in tumor modeling.[38]

3. Bioprinting-based tumor model construction for HNSCC

Recent advances in bioprinting have enabled the creation of complex tumor models that closely replicate the tumor microenvironment. For instance, multi-material bioprinting integrates various cell types and biomaterials, accurately reflecting the cellular diversity and structural complexity of HNSCC tumors.[21] Material selection is a critical aspect of bioprinting tumor models, as bioinks that mimic the tumor extracellular matrix (ECM) significantly affect cell behavior and functionality (Figure 3). Studies show that bioinks combining natural polymers with decellularized ECM components enhance cell viability and tissue maturation.[39] Patient-specific bioinks, such as those derived from platelet-rich plasma, improve bioactivity for personalized medicine.[40] Furthermore, the incorporation of dynamic culture systems, such as perfused bioreactors, can enhance bioprinted tumor models by providing a realistic physiological environment. These systems ensure a continuous supply of nutrients and oxygen, as well as the efficient removal of waste, thereby supporting the growth and maintenance of intricate tumor structures.[41]

3.1. Cell selection of HNSCC

3.1.1. Selection criteria for primary cells and cell lines

The initial phase in the construction of an HNSCC tumor model involves the selection of appropriate cell lines. Primary cells and established cell lines present distinct advantages and limitations, respectively. Primary cells, derived directly from patient tumor tissues, offer a more accurate representation of tumor biology by preserving the characteristics of the tumor microenvironment. Nonetheless, the isolation and culture of primary cells are challenging, and these cells exhibit limited proliferative capacity, typically sustaining viability *in vitro* for only a brief duration. In contrast, cell lines demonstrate enhanced proliferative abilities and reproducibility, rendering them more suitable for large-scale experimental applications.[42,43] Frequently utilized HNSCC cell lines, such as HSC-3 and SCC-25, have undergone numerous passages and exhibit favorable growth characteristics and stability. When selecting an appropriate cell line, it is essential to consider not only its intrinsic biological characteristics but also its responsiveness to therapeutic agents.[18] For instance, research has demonstrated that certain cell lines exhibit varying sensitivities to chemotherapeutic agents, potentially attributable to differences in their gene expression profiles and metabolic properties.[44] Furthermore, the culture conditions of cell lines are critically important, often necessitating the incorporation of growth factors into a specific medium to facilitate cell proliferation and survival. Recently, the implementation of 3D cell culture technology has offered a novel perspective for HNSCC research. These

Table 2. Three common types of bioprinting technology

Type	Advantages	Limitations
Inkjet printing	• High resolution • Rapid printing speed	• Stringent bioink conditions
Extrusion printing	• Fabricating larger structures for complex tissue and organ	• Low resolution
Laser-assisted printing	• Accurately deposit biological materials at specified locations	• Time-consuming • Relatively high cost • Affecting cell activity

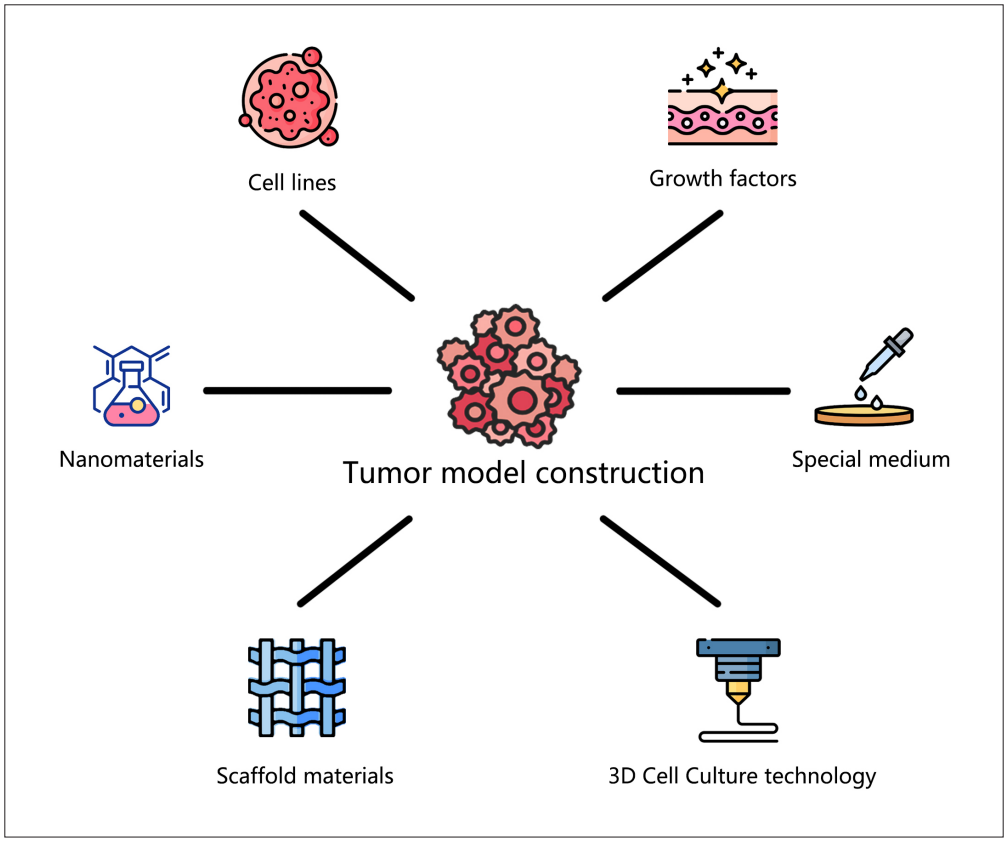

Figure 3. Essential factors for bioprinting-based HNSCC tumor model construction, involving cell lines, printed materials, and construction methods. Abbreviation: HNSCC, head and neck squamous cell carcinoma.

3D models are capable of more accurately replicating the tumor microenvironment, thereby enhancing the physiological relevance of experimental studies.[45]

3.1.2. Role of cancer stem cells in the model construction

Cancer stem cells (CSCs) are integral to the development of models for HNSCC. These cells possess the capacity for self-renewal and differentiation, thereby facilitating tumor initiation, progression, and metastasis. Research indicates that CSCs in HNSCC are closely linked to tumor drug resistance, recurrence, and metastasis.[46,47] When developing *in vitro* models of HNSCC, the selection of cell lines or primary cells enriched with CSCs can more accurately replicate the heterogeneity and complexity of tumors. These models are instrumental not only in advancing the understanding of tumor biology but also in facilitating the screening of novel therapeutic targets and assessing drug efficacy. For instance, employing markers specific to CSCs enables the screening of cell populations that are responsive to particular treatments, thereby laying the groundwork for personalized therapeutic approaches.[48,49]

3.2. Selection and characteristics of printed materials

Biomaterials are crucial in the development of HNSCC tumor models. Various factors are taken into consideration when selecting biomaterials, such as biocompatibility, mechanical properties, and cellular interactions. Recently, researchers have increasingly recognized the potential of ECM-derived materials in tissue engineering and regenerative medicine, as they can offer growth conditions for tumor cells that more closely mimic the *in vivo* environment.[50–52] For instance, scaffold materials fabricated from polymers can improve cell adhesion and proliferation, thereby more accurately replicating the tumor microenvironment. Furthermore, the incorporation of nanomaterials presents novel opportunities for HNSCC research. Specifically, gold nanostructures have been utilized in conjunction with chemotherapy and photothermal therapy, demonstrating promising therapeutic outcomes.[53] In summary, the choice and application of biomaterials not only influence cellular

behavior but also directly impact biological characteristics and potential for clinical translation.

In the selection of biomaterials, natural and synthetic biomaterials each have their own unique advantages and disadvantages, as shown in Table 3. Natural biomaterials usually have good biocompatibility and biodegradability, and can interact well with the biological environment, which prompts their widespread utilization in tissue engineering and regenerative medicine. For example, materials derived from the ECM perform well in promoting cell attachment and proliferation, effectively supporting tissue regeneration.[50] However, the acquisition and processing process of natural materials may lead to batch-to-batch differences that can affect their performance. Moreover, certain natural materials may trigger immune responses, limiting their clinical applications. By contrast, synthetic biomaterials have their tunability and replicability. By changing the synthesis conditions, the physical and chemical properties of the material can be precisely controlled to meet specific application requirements. For example, synthetic polymers such as polylactic acid (PLA) show good mechanical properties and controlled degradation rates in biomedical applications.[54] However, synthetic materials often lack the biological activity inherent to natural materials and may cause poor cell attachment and proliferation. Therefore, many researchers are exploring composites that combine natural and synthetic materials in the hope to exert the advantages of both and overcome their respective defects.[55]

In the biomedical field, biocompatible materials that combine natural and synthetic materials have important implications for tissue engineering and regenerative medicine. For instance, the PLA and gelatin materials are widely used in 3D printing technology because of their good biocompatibility and biodegradability. PLA is a synthetic polymer with excellent mechanical properties and relatively fast biodegradation rates and is suitable for the fabrication of scaffold materials to support cell attachment and growth. Moreover, gelatin, as a natural polymer, is favored for its good interaction with cells and is able to promote cell proliferation and differentiation. Studies have shown that the composite material of PLA and gelatin can effectively improve the mechanical properties and biological activity of the scaffold, thus providing a better microenvironment for tissue regeneration.[56,57] In addition, the selection of biocompatible materials should also consider their stability in the *in vivo* environment and the impact of degradation products on the surrounding tissues to ensure their safety and efficacy in clinical applications.[58,59]

A bioink should replicate the mechanical and biochemical properties of the tumor microenvironment. For instance, a decellularized extracellular matrix (dECM)-based composite hydrogel bioink can effectively mimic HNSCC properties *in vitro*, offering suitable mechanical strength and biological activity to support cell proliferation and organization.[51] Additionally, ECM-based biomaterials are widely used in studies of HNSCC for their ability to provide a suitable environment for cell attachment and proliferation.[60] These materials are able to effectively support the growth and migration of the tumor cells, and thus more truly reflect the biological characteristics of the tumor. In addition, synthetic polymers such as polyvinyl alcohol (PVA) and PLA were also used in the construction

Table 3. Comparison of natural and synthetic biomaterials

Criteria	Natural biomaterials	Synthetic biomaterials
Biocompatibility and interaction with biological environments	• Good	• Poor
Biodegradability and degradation products	• Good biodegradability with usually non-toxic degradation by-products that can be metabolized by the body.	• Precisely controlled biodegradability with potentially toxic degradation by-products that are less easily metabolized
Performance consistency	• Potential for batch-to-batch variability due to source material difference	• High replicability and consistency
Risk of triggering immune response	• High	• Low
Cell interaction	• Excellent cell attachment and proliferation	• Often lack intrinsic biological activity
Customizability	• Limited tunability of physical and chemical properties	• Highly tunable
Mechanical properties	• Can be unstable	• Good applicability
Clinical applications	• Widespread used in tissue engineering and regenerative medicine	• Commonly used for applications requiring precise control over material

of HNSCC models. These materials can not only provide good supporting structures but also control the growth and spread of tumor cells by regulating their degradation rate.[61] For example, studies have shown that the utilization of functionalized polymer materials can effectively promote the proliferation of tumor cells and provide a good platform for drug screening and therapeutic efficacy evaluation.[62] Overall, the selection of appropriate biomaterials is crucial for constructing HNSCC models, which not only affects the biological characteristics of the model but also is directly related to the reliability of research results and the potential for clinical translation. With the development of biomaterials science, more new materials will be developed in the future to better serve the research and treatment of HNSCC.

The mechanical properties and biological activity of cell scaffold materials are key factors influencing their application in tissue engineering. The scaffold material should have sufficient mechanical strength to withstand physiological loads, and its elastic modulus should be matched with the target tissue to promote cell adhesion, proliferation, and differentiation.[57,63] For example, nanocrystalline metal materials have received much attention in biomedical applications recently due to their superior mechanical properties and biocompatibility. It has shown that titanium alloy with nanostructure shows excellent biocompatibility and biological activity in bone tissue engineering, which can effectively promote osteocyte proliferation and mineralize.[59,64]. Moreover, the pore structure and surface properties of the scaffolds also have significant effects on cell behavior, and optimizing the microstructure of the scaffold can improve cell permeability and nutrient exchange, thus enhancing the effect of tissue regeneration.[58,65] Therefore, a combination of mechanical properties, biocompatibility, and effects on cell behavior are needed to design cell scaffold materials to achieve optimal regeneration results.

3.3. Construction methods for the HNSCC tumor model

HNSCC is a highly heterogeneous malignancy, and the construction of an effective tumor model is crucial for studying its biological characteristics and treatment strategies. The construction methods of tumor models mainly include single-cell models and multicellular models, each of which has unique advantages and application scenarios.

Single-cell models are used to examine tumor cells' individual behavior and gene expression, allowing precise analysis of genomic and transcriptomic data to uncover tumor heterogeneity sources and mechanisms.[66] The HNSCC tumor microenvironment, rich in diverse immune cells, influences patient outcomes and treatment responses.[67] Single-cell RNA sequencing uncovers the cellular makeup and features of these tumors and their surroundings.[68] Immunoinfiltration in HNSCC correlates with patient survival and treatment efficacy. Researchers used single-cell transcriptome data to identify immune genes linked to HNSCC prognosis and developed a predictive model for survival and treatment outcomes.[69] In contrast, multicellular models have a higher resemblance to tumor microenvironment, especially in terms of intercellular interactions and signaling. For example, the application of 3D cell culture and bioprinting allows researchers to construct tumor models closer to *in vivo* conditions that show higher biological relevance in drug sensitivity testing and tumor microenvironment studies.[70] Sun et al.[71] has successfully established colorectal cancer (CRC) and colorectal cancer liver metastasis (CRLM) tumor model by utilizing 3D bioprinting technology, which effectively retains parental tumor biomarkers and mutation profiles, implying their broad application in precision chemotherapy prediction and preclinical research. By combining the advantages of these two models, future studies may provide a more comprehensive understanding of the biology of HNSCC (see Table 4). Selecting the

Table 4. Comparison of the construction for the single-cell and multicellular bioprinting models

Characteristics	Single-cell models	Multicellular bioprinting models
Main advantages	• Cheaper and readily available	• Higher biological relevance in drug sensitivity testing
Technical foundation	• Single-cell RNA sequencing	• 3D cell culture and bioprinting technologies
Biological relevance	• Highly specific, capable of parsing individual cell behavior and function	• Higher overall biological relevance, especially in simulating complex tumor microenvironments
Research focus	• Gene expression patterns and molecular mechanisms at the single-cell level	• Intercellular interactions, tissue structure, and how these factors influence tumor development and treatment response

appropriate cell type is crucial for effective modeling. Research indicates that patient-derived organoids and xenograft models more accurately reflect the heterogeneity and treatment response of HNSCC, offering greater clinical relevance and aiding in the creation of personalized treatment strategies.[72]

The growth conditions and the culture environment of the HNSCC tumor model are crucial for the validity of the model. In a single-cell model, the growth environment of a cell needs to mimic the *in vivo* microenvironment as much as possible to ensure that the physiological properties and functions of the cell are preserved.[73] For example, the use of specific media components and growth factors can promote the proliferation and survival of tumor cells while maintaining their original gene expression profile.[74] In multicellular models, the choice of biomaterials and 3D culture systems are equally important, as they provide appropriate mechanical and chemical signals that promote cell self-organization and functional performance.[75] Moreover, the dynamic balance of oxygen, nutrients, and waste in the tumor microenvironment also needs to be considered to avoid cellular hypoxia or nutrient deficiency, which has a significant impact on the growth of tumor cells and drug response.[76]

3.4. Optimization of the printing process

In the 3D printing technology, the optimization of the printing parameters is crucial for cell viability, as shown in Table 5. Studies have shown that factors such as printing pressure, speed, and temperature all significantly affect cell survival and function. For example, too high a printing pressure may lead to mechanical damage during the printing process, which reduces cell survival. Some studies have shown that appropriate printing pressures (e.g., <400 hPa) can significantly improve cell survival while maintaining printing accuracy, especially when using biomaterial-based hydrogels.[77] In addition, the choice of printing speed is also crucial. Too fast speed may lead to uneven flow of material, which may affect the distribution and survival of cells. In terms of temperature, studies have shown that appropriate printing temperatures (such as 37 °C) can improve cell activity and proliferation capacity, especially in hydrogels used in bioprinting.[78]

Print path design is an important factor affecting cell arrangement and tissue structure. With the rational design of printing paths, a precise arrangement of cells can be achieved to better model the structure and function of biological tissues. For example, the adoption of specific printing paths (such as parallel lines or honeycomb structures) can effectively control the spatial distribution of cells and promote cell–cell interactions and signaling.[79] Some studies have explored the influence of different printing pathways on cell arrangement and found that optimized printing path design can improve cell survival and functions.[80] Moreover, employing multilayer printing techniques can achieve a heterogeneous distribution of cells at different levels, which is crucial for constructing complex models of biological tissues. Future studies should continue to explore the relationship between print pathway design and cell arrangement to advance the application of bioprinting in tissue engineering and regenerative medicine.

In summary, the construction of bioprinting-based tumor models for HNSCC involves a multifaceted approach that encompasses advanced bioprinting techniques, careful material selection, and the incorporation of dynamic culture systems. The integration of bioprinting into HNSCC research is anticipated to potentially lead to more effective treatments for patients.

4. Tissue structure and microenvironment reconstruction for HNSCC tumor model

4.1. Reconstruction of tissue structure and microenvironment

A bioprinted tissue structure and microenvironment in head and HNSCC tumor model are crucial. This process involves using the precise combination of biomaterials and living cells to model the complexity of the tumor microenvironment.[81] Through 3D bioprinting, it is possible

Table 5. Challenges in clinical transformation

Aspect	Challenges
Technological complexity	• Intricate technology and varied clinical requirements make the translational process complex • Unresolved issues in material chemistry and long-term stability for neural interface technology
Regulatory and ethical considerations	• Lengthy and intricate approval processes can delay market entry • Regulatory and ethical frameworks need enhancement
Funding access	• Insufficient financial support can stagnate innovative projects

to create tumor models with multilevel structure that contain not only tumor cells but also multiple components, such as stromal cells, endothelial cells, and immune cells. This multicellular co-culture method can more truly reflect the biological characteristics of the tumor and the dynamic changes in the microenvironment.[22] In addition, bioprinting allows the introduction of bioactive factors and ECM components in tumor models to promote cell growth and differentiation. This approach is able to efficiently mimic key processes such as angiogenesis, cell migration, and invasion, thus, providing an ideal platform for studying tumor progression and metastasis.[82] Further optimization of these bioprinted models enables more precise control of the tumor microenvironment, thereby improving the efficacy and reliability of drug screening.[83] For instance, research has demonstrated that the bioprinted HNSCC model can accurately replicate the spatial distribution and functional interactions of various cell types within the tumor microenvironment, thereby influencing tumor growth and metastatic behavior.[52] Through 3D bioprinting technology, multiple cell types can be integrated into scaffold-free tumor tissues, forming a tumor microenvironment with specific structures. This method not only simulates patient-specific tumors but also allows for the evaluation of tumor intrinsic and extrinsic properties using the patient original tissue.[84] In addition, the bioprinted HNSCC model can be used to study the interactions between tumor cells and normal adjacent tissues, particularly their behavior at the frontiers of invasive tumors. By integrating the human cancer cell line FaDu into an oral mucosa tissue model, clusters of invasive tumor cells that penetrate the basement membrane and invade the lamina propria can be observed. This model offers potential for further investigation into the invasiveness of cancer cells.[85] Furthermore, this model can be employed to assess the efficacy of diverse treatment strategies, offering more realistic predictive outcomes and thereby enhancing support for clinical applications.[86]

The tumor microenvironment of HNSCC consists of tumor, stromal, and immune cells. Tumor cells, which are the primary component, display heterogeneity and invasiveness, influencing growth and metastasis.[87–89] Stromal cells, especially cancer-associated fibroblasts (CAFs), play a vital role in the tumor microenvironment by releasing growth factors and cytokines that boost tumor cell growth and migration.[90] Immune cells like tumor-infiltrating lymphocytes, regulatory T cells, and natural killer cells are crucial in HNSCC, with their infiltration levels affecting patient prognosis.[91]

4.1.1. Importance of extracellular matrix components

ECM is a key component of the tumor microenvironment, which plays an important role in supporting, signaling, and regulating cell behavior. Studies have shown that tumor development is closely related to the composition and structure of the ECM. ECM changes in the tumor microenvironment, such as the increase and decrease of composition and changes in the degree of crosslinking, directly affect the growth, migration, and invasion capacity of tumor cells.[92] In addition, components in ECM, such as collagen, fibronectin, and glycosaminoglycan, not only provide physical support for tumor cells, but also participate in cell–cell interactions as signaling molecules and regulate the communication between tumor cells and surrounding cells.[93,94]

A bioink should replicate the mechanical and biochemical properties of the tumor microenvironment. For instance, a dECM-based composite hydrogel bioink can effectively mimic HNSCC properties *in vitro*, offering suitable mechanical strength and biological activity to support cell proliferation and organization. In a study by Kort-Mascort et al.,[52] a novel printable biogel containing alginate and gelatin as rheological modifiers was developed, which conferred mechanical integrity to the bioactive acellular ECM (dECM) derived from the porcine tongue after decellularization and lysis. The morphological features of the bioink revealed a fiber network with nanoscale pores. The immortalized cell lines UM-SCC-12 (laryngeal carcinoma) and UM-SCC-38 (oropharyngeal carcinoma) were selected as cellular components. The disk-shaped model, with a diameter of 5 mm and a height of 500 μm, was printed using extrusion printing. The model is highly reproducible, enabling HNSCC cell proliferation and recombination processes, and maintaining cell viability above 90% over the past 3 weeks. On the 15th day of culture, the cells produced spheroids with a cross-sectional area of at least 3000 μm^2 and were positive for cytokeratin. The resulting 3D model was utilized to evaluate tumor cells' response to cisplatin and 5-fluorouracil.[51] The authors have recently published data on the improved HNSCC 3D model, where they represent the cellular components with two types of cells, namely UM-SCC-38 and A8-HVFFs (immortalized human vocal cord fibroblasts) at a ratio of 1:2.[52] While creating the model through culturing, the researchers observed development and growth of spheroids over time, with cancer cells at the core and fibroblasts at the periphery. It can be concluded that HNSCC's 3D-bioprinted model is essentially an improved tissue engineering model using hydrogel as a scaffold, and improved printing methods rather than the usual method of gel stratification on the substrate are applied to allow more accurate control of tissue structure in compliance with specified parameters. So far, bioprinted HNSCC models have been from immortalized cell lines

due to the need to use large numbers of cells to obtain the desired results.

In the process of reconstructing the HNSCC tumor microenvironment *in vitro*, it is crucial to consider the biocompatibility of bioinks, their shape fidelity, and long-term stability. Gelatin methacryloyl (GelMA) is known to enhance biomechanical properties and shape fidelity; however, it may elicit immune responses that adversely affect cell interactions within 3D-bioprinted tumor models. Conversely, carboxyl-NC bioink, which supports the survival, proliferation and maintenance of the epithelial phenotype of HNSCC cells, demonstrates superior bioprinting capabilities, enhanced biocompatibility, and reduced immunogenicity. These attributes render carboxyl-NC bioink a promising alternative to GelMA for high-throughput preclinical drug trials.[95]

In the selection of bioinks, it is also imperative to evaluate their photopolymerization properties to ensure adequate mechanical stability and effective cell encapsulation during the printing process. Photopolymerizable bioinks are capable of forming high-resolution and mechanically robust structures during 3D printing, which are essential for investigating cell–cell and cell–matrix interactions within the tumor microenvironment.[52,97–98]

4.1.2. Cell–cell interactions and their effects on tumor biological properties

Cell–cell interactions play a crucial role in the tumor microenvironment. These interactions affect proliferation, survival, and metastatic capacity of tumor cells through multiple signaling pathways. The interaction between tumor cells and CAFs, immune cells, and other components of the tumor microenvironment can promote tumor progression and metastasis. For example, CAFs promote tumor growth and metastasis by secreting cytokines and growth factors, altering immune characteristics of the tumor microenvironment, and suppressing anti-tumor immune response.[99,100] In the HNSCC, CAFs elevate extracellular lactate by secreting hepatocyte growth factor, creating a metabolic symbiosis with HNSCC cells through bidirectional signaling with basic fibroblast growth factor, which presents a potential therapeutic target.[101] Additionally, the invasion of HNSCC cell lines CAL33 is likely aided by CAFs remodeling the ECM via matrix metalloproteinases. Additionally, CAFs enhance tumor cell invasion depending on the collagen density distribution in the culture.[102] Moreover, cell–cell signaling involves interactions between cell-surface receptor and ligand that are able to regulate cell behavior and fate, which in turn affect the biology of the tumor.[103] Inclusion of tumor-associated fibroblasts and immune cells in bioprinted constructs alters signaling pathways supporting tumor survival and growth.[104]

Recent advancements in 3D bioprinting technology have enabled the creation of bioengineered tumor models that closely mimic the tumor microenvironment, incorporating various cell types, including CAFs and immune cells.[105] CAFs are known to play a pivotal role in the tumor microenvironment (Figure 4), influencing tumor growth, invasion, and metastasis through their interactions with cancer cells and immune cells.[106] They contribute to the ECM deposition and remodeling, which

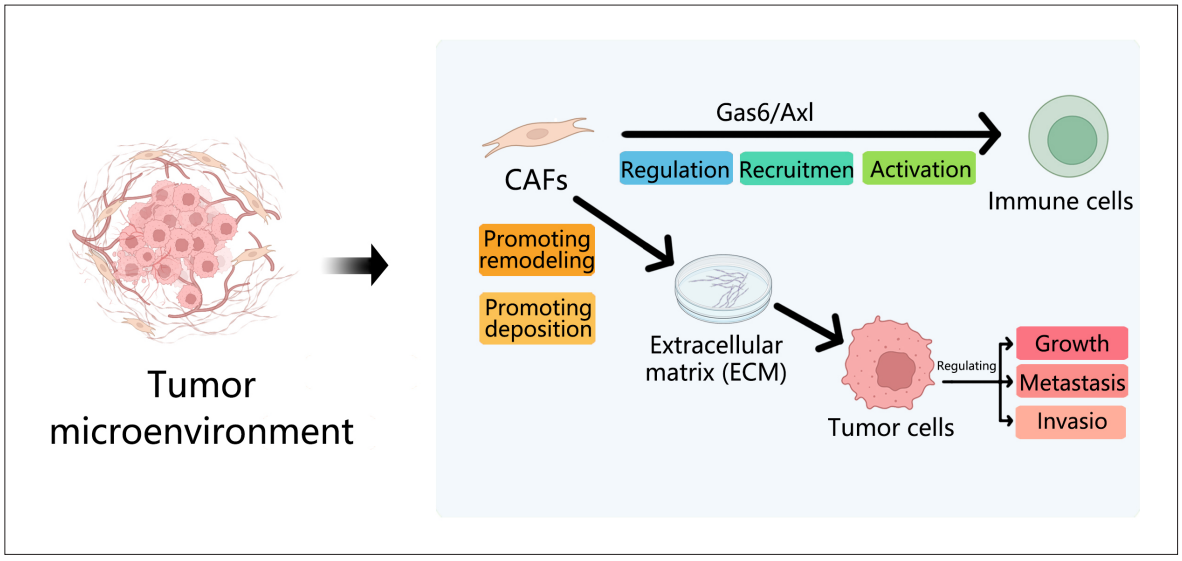

Figure 4. Role and mechanisms of cancer-associated fibroblasts (CAFs) in the tumor microenvironment, including regulating cell activities in tumor cells and surrounding immune cells in the cytoplasm.

can alter the mechanical properties of the tumor stroma, thereby affecting tumor cell behavior and therapeutic responses.[107] Moreover, CAFs can modulate immune cell recruitment and activation, creating an immunosuppressive environment that supports tumor survival.[108] By integrating CAFs and immune cells into bioprinted constructs, researchers can investigate how these interactions impact signaling pathways that promote tumor cell survival and resistance to therapies. For instance, the Gas6/Axl signaling pathway, which is implicated in immune evasion and tumor progression, may be influenced by the presence of CAFs in these models.[109]

Understanding these dynamics is essential for developing targeted therapies that can disrupt the supportive roles of CAFs and enhance the efficacy of immunotherapies.[110] Furthermore, the functional diversity and phenotypic plasticity of CAFs highlight the need for a nuanced approach in designing bioprinted models that accurately reflect the heterogeneity of tumors.[106] This could lead to more effective personalized treatment strategies, as these models allow for high-throughput drug screening and the identification of specific therapeutic targets within the tumor microenvironment.[105] Ultimately, the incorporation of tumor-associated fibroblasts and immune cells into bioprinted constructs represents a promising avenue for advancing our understanding of cancer biology and improving therapeutic outcomes.

By constructing a 3D microenvironment with physiological relevance, researchers are able to observe tumor cell proliferation, migration, and apoptosis under different conditions. Such a model can better reflect the true response of tumor cells *in vivo*, especially in the context of drug treatment and immunotherapy.[111] For example, tumor models constructed using bioprinting technology can be experimented in a dynamic fluid environment, so that the effect of blood flow on tumor cell behavior can be simulated. Studies show that tumor cells exhibit increased invasiveness and tolerance to drugs in bioprinted vascularization models, providing new perspectives on understanding the resistance mechanisms in tumors.[112] Moreover, these models can also be used to evaluate the effects of different treatment options, helping in the development of personalized cancer treatment strategies.[113] Using these 3D models, simulating an oxygen deficiency condition may help decipher the mechanism by which tumor cells can adapt to low oxygen conditions. It is a common characteristic of solid tumors and is known to contribute to treatment resistance.[114]

4.2. Simulation of the tumor cell behavior

In biomedical research, the bioprinted HNSCC tumor model offers substantial advantages in replicating tumor cell behavior. These models effectively mimic the growth patterns, migration, and invasion characteristics of tumor cells *in vivo*. By modulating the cell types and matrix components utilized in the bioprinting process, researchers can investigate the adaptive responses of tumor cells within various microenvironments. Tumor cells exhibit more complex behaviors in 3D-bioprinted environments compared to traditional 2D cultures, including cell aggregation, morphological transformations, and intercellular signaling.[115,116] This dynamic simulation of cellular behavior offers novel insights into the biology of HNSCC and its therapeutic responses. Furthermore, bioprinting models facilitate the examination of interactions between tumor cells and immune cells, bearing significant implications for the advancement of innovative immunotherapeutic strategies.[117,118] By conducting an in-depth analysis of these cellular behaviors, researchers can enhance their understanding of tumor progression mechanisms and contribute to the development of personalized treatment options.

Research has shown that the composition of bioprinted materials, such as collagen and hyaluronic acid, can significantly influence cellular interactions and responses.[119] Additionally, nanoscale features in bioprinted constructs enhance cell adhesion and differentiation, demonstrating the importance of material selection.[120] Dynamic mechanical stimulation further affects tumor behavior, and devices that apply mechanical forces provide insights into how these stimuli modulate cancer cell functions.[121] Moreover, integrating micropatterning techniques within bioprinting allows for the exploration of cellular interactions, revealing that spatial organization impacts cellular responses.[122] Techniques such as optically-induced electrokinetics enable controlled growth of cancer cells in engineered environments.[123]

Bioprinting facilitates a detailed understanding of the complex biochemical and mechanical cues driving cancer biology. For instance, the incorporation of hydrogels that replicate the ECM components can significantly influence cellular responses. A comparative study demonstrated that chondrocytes and osteoblasts exhibited enhanced proliferation and functionality when cultured on hydrogels composed of their native ECM components, highlighting the importance of biochemical cues in guiding cell behavior.[119] Moreover, the ability to pattern hydrogels using bioprinting systems has shown that cellular interactions and morphology are highly dependent on the specific cell types involved. A study reported that human mesenchymal stem cells (hMSCs) formed aggregates in patterned hydrogels, while fibroblasts and endothelial cells displayed different growth behaviors, emphasizing the role of biochemical signals in modulating cell fate.[122] The dynamic

control of hydrogel properties through optically induced electrokinetics has been explored to manipulate breast cancer cell growth patterns, demonstrating how biophysical cues can complement biochemical signals to influence cellular outcomes.[123] The integration of biophysical and biochemical cues through bioprinting not only enhances our understanding of cancer cell behavior but also paves the way for developing more effective therapeutic strategies. By creating 3D models that accurately reflect the tumor microenvironment, researchers can better investigate the mechanisms underlying cancer progression and treatment resistance, ultimately leading to improved patient outcomes in cancer therapy.[120,121]

5. Applications in clinical practice

Through precise bioprinting techniques, 3D cellular models that closely mimic the human physiological environment can be developed, thereby facilitating a more accurate evaluation of drug responses. These models are capable of simulating the distribution and metabolism of pharmaceuticals within the body, as well as reflecting cell–cell interactions and the influence of the microenvironment. Research indicates that bioprinting technology enhances the efficiency of drug screening, diminishes reliance on animal testing, and partially lowers drug development costs. For instance, a tumor-chip platform constructed via bioprinting technology can assess the pharmacokinetics and therapeutic responses of drugs under dynamic culture conditions, thereby yielding more realistic drug response data.[124] Furthermore, bioprinting technology can be integrated with other methodologies, such as microfluidic technology, to further augment the accuracy and reliability of drug screening processes.[125]

5.1. Assessment of drug response

The application of bioprinted models in drug response assessment is gaining increasing attention. Traditional 2D cell culture models often fail to accurately reflect the true effect of drugs in the body, while bioprinting technology can better simulate the metabolism and efficacy of drugs in living organisms by constructing a 3D structure. For example, studies have shown that tumor models constructed using bioprinting technology can effectively predict patient response to chemotherapeutic agents.[126] These models can not only provide quantitative data on drug inhibition of tumor cell growth but also reveal the mechanism of drug action and provide the basis for individualized treatment.[127] In addition, bioprinted models are also used in high-throughput drug screening, enabling rapid assessment of the efficacy and safety of multiple drugs, thus accelerating the development process of new drugs.[128]

In the assessment of drug response, the utilization of bioprinting introduces innovative approaches to drug development in HNSCC therapy. The application of 3D bioprinting technology allows for the creation of biomimetic organ models that closely mimic human physiology, which is crucial for understanding the complex interactions within tumors and their microenvironments.[129] Recent studies have demonstrated that tumor organoids can effectively capture the genetic and molecular diversity of HNSCC, providing a platform for *in vitro* drug screening.[130] By utilizing these organoids, researchers can evaluate the efficacy of various therapeutic agents, including those not typically used in clinical practice, thereby expanding the repertoire of potential treatments available for HNSCC patients. Furthermore, the integration of 3D bioprinting in drug discovery processes can streamline the development pipeline, allowing for rapid testing and optimization of drug formulations and delivery systems.[131] The incorporation of advanced bioprinting techniques into clinical workflows may significantly enhance the efficiency and success rates of drug development, particularly in oncology.[132]

Research indicates that brain microenvironment models developed through bioprinting technology serve as effective tools for assessing drug responses in neurological disorders, thereby offering crucial data to support the advancement of neural pharmacotherapy.[133] Furthermore, bioprinting technology facilitates the evaluation of synergistic effects among various drug combinations, aiding researchers in identifying optimal treatment strategies and enhancing the efficacy of personalized medicine.[134] The advent of 3D bioprinting has revolutionized the way researchers can create biomimetic organ and disease models, which are crucial for understanding drug interactions and responses in a more physiologically relevant context.

Unlike traditional 2D cultures and animal models, 3D-bioprinted models can closely mimic human physiology, thereby enhancing the accuracy of drug efficacy and safety evaluations.[131] The integration of 3D bioprinting in drug discovery allows for high-throughput screening systems that can rapidly assess the effects of various compounds on disease models. This capability not only accelerates lead identification but also provides data that better reflects clinical outcomes, which is essential for the development of effective therapeutics.[135] Furthermore, the potential of bioprinting extends to the production of vaccines and therapeutics, where its versatility can be harnessed to develop innovative delivery systems that improve patient compliance and treatment outcomes.[129] As the field of bioprinting continues to evolve, it is poised to play a pivotal role in modernizing drug development paradigms, ultimately leading to more effective and personalized therapeutic strategies.[136,137]

5.2. The potential of individualized treatment

In addition to improving the drug discovery process, bioprinting technology also facilitates the creation of personalized medicine solutions. By enabling the fabrication of complex drug delivery systems tailored to individual patient needs, bioprinting can enhance drug absorption and bioavailability while minimizing adverse reactions.[138,139] This personalized approach is particularly beneficial for sensitive patient populations, such as pediatric and geriatric groups, who often require specialized formulations. The potential of bioprinting technology in personalized therapy is becoming increasingly evident. By utilizing bioprinting techniques with patient-derived cell samples, it is possible to create individualized tissue models that more accurately reflect the patient's physiological characteristics and disease status during the drug screening process. This personalized approach to drug screening not only enhances the efficacy of pharmaceuticals but also minimizes adverse side effects. Research indicates that bioprinting utilizing patient-derived stem cells offers tailored treatment options for individual patients, thereby significantly improving therapeutic success rates.[140]

Furthermore, bioprinting technology can be integrated with digital technology to enhance the optimization of individualized treatment plans through data analysis and artificial intelligence algorithms, thereby advancing the objectives of precision medicine.[141] The implementation of this approach not only enhances treatment efficacy but also offers more personalized medical services to patients, signifying the advent of a new era in individualized healthcare.

5.3. Call for development of application guidelines

In addition to the technical aspects, it is essential to establish comprehensive application guidelines for bioprinting in the context of HNSCC. These guidelines should encompass the meticulous selection of appropriate bioinks, the strategic design of scaffolds, and the rigorous evaluation of bioprinted constructs in terms of their mechanical and biological properties.[142] The development of standardized protocols will ensure the consistency, reproducibility, and reliability of the bioprinting process in HNSCC applications, ultimately facilitating their translation into clinical practice.[143] As the field of bioprinting continues to evolve, it is crucial to address the ethical considerations and regulatory frameworks surrounding the use of engineered tissues in clinical settings.[143] Establishing clear guidelines will help navigate the complexities of bioprinting technologies, ensuring that they are safely and effectively integrated into therapeutic protocols for HNSCC. Thus, bioprinting is a promising approach for treating HNSCC, potentially transforming personalized medicine through custom tissue constructs. Developing comprehensive application guidelines is essential to maximize its clinical potential (Figure 5).

6. Future challenges and recommendations

6.1. Improvement and innovation of technology

Technological advancements and innovations are pivotal in the medical domain, particularly concerning treatment and diagnosis. In recent years, the swift progression of biotechnology and information technology has catalyzed continuous innovation in related medical technologies. For instance, the emergence of nanomedicine offers novel solutions to combat antimicrobial resistance by employing nanoparticles to target specific cells, thereby enhancing therapeutic efficacy and minimizing side effects.[144] Advancements in research on selective organ-targeted nanoparticles are enhancing drug delivery efficiency while minimizing distribution to non-target tissues, thereby augmenting clinical efficacy.[145] Nonetheless, despite ongoing technological progress, numerous challenges persist in the clinical translation process, including issues related to biocompatibility, drug release mechanisms, and cost-effectiveness.[146] Consequently, future investigations should prioritize assessing the feasibility and safety of this technology to ensure its seamless integration into clinical practice.

6.2. Prospects and obstacles to clinical transformation

Clinical transformation serves as a crucial intermediary in translating fundamental research findings into practical medical treatments. While it holds significant potential, this process encounters several challenges, as summarized in Table 5. Primarily, the intricate nature of the technology and the varied clinical requirements render the translational process exceedingly complex. For instance, despite the significant advancements achieved in neural interface technology at the laboratory stage, issues related to material chemistry and long-term stability remain unresolved in clinical applications.[147] Secondly, regulatory and ethical considerations are impediments to clinical translation of new technologies. The approval process for these innovations is frequently protracted and intricate, potentially delaying their timely market entry. Furthermore, access to funding constitutes a critical factor, as numerous innovative projects experience stagnation due to insufficient financial support.[148] Consequently, future research requires not only technological advancements but also comprehensive improvements in policy, funding, and ethical frameworks to enable the efficient clinical translation of these innovations.[149]

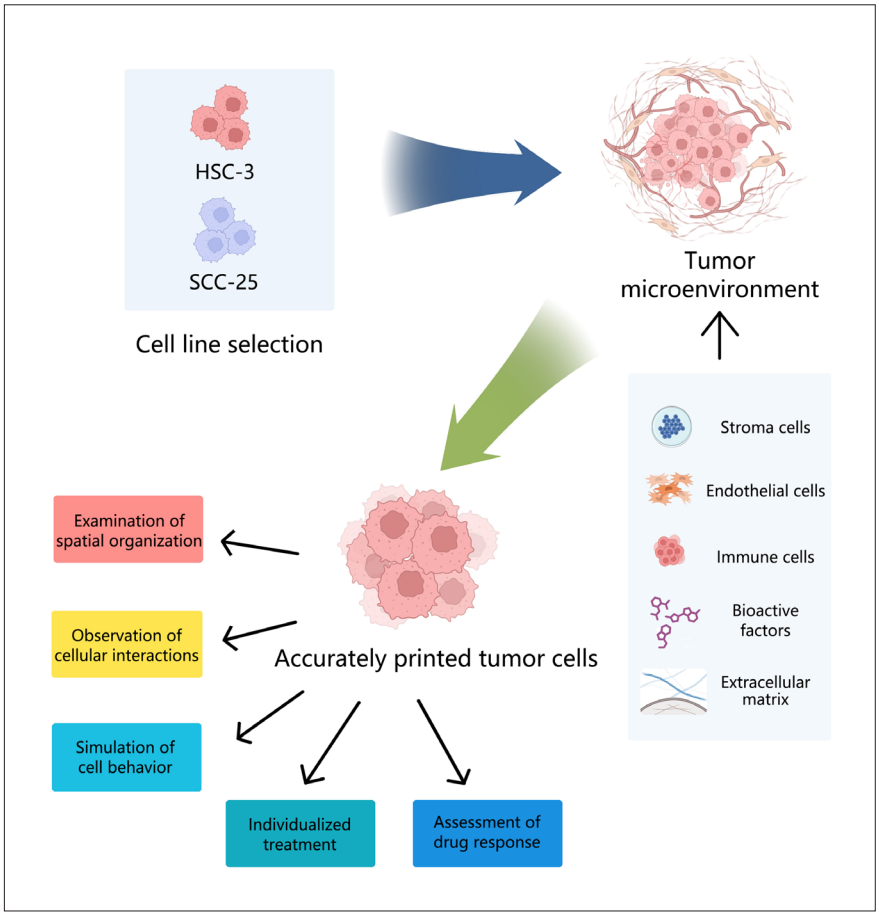

Figure 5. Establishment of HNSCC tumor model through cell line selection, tumor microenvironment mimicry, and its various applications. Abbreviation: HNSCC, head and neck squamous cell carcinoma.

Bioprinting technology shows great potential in the construction of tumor models, but it still faces many challenges in the process of clinical transformation. Currently, research on bioprinted HNSCC tumor models has focused on how to better simulate the tumor microenvironment in order to provide a more realistic *in vitro* model[23] for drug screening and treatment effect evaluation. Despite some progress, the following key issues need to be addressed for clinical application.

Firstly, current bioprinting techniques have some limitations in printing accuracy and biomaterials selection. Although multiple bioinks have been developed, further optimization in terms of biocompatibility and functionality is needed.[32] The success of bioprinting depends on the properties of the bioink, including its rheology, mechanical properties, and biological properties.[150] For example, the printing performance of the bioink directly affects the shape fidelity of the printed structure and the viability of the cells.[151]

Furthermore, existing bioinks often fail to meet the needs of complex tissue engineering, especially[152] in simulating the cell microenvironment and promoting cell proliferation. The tumor microenvironment of HNSCC is a complex and dynamic network that continually changes its composition and state.[153,154] While the complexity and heterogeneity of the tumor microenvironment are among the main obstacles to the clinical translation of bioprinted HNSCC models. Studies have shown that the tumor microenvironment of HNSCC not only affects tumor growth and invasiveness but also influences the effectiveness of treatment.[72] Tumorigenesis *in vivo*, including tumor cells' interaction with the immune system, is an intricate process that is regulated by both genetic and epigenetic factors.[155] In HNSCC, the characteristics of tumor microenvironment include hypoxia, immunosuppression, and high density of tumor-associated fibroblasts. Hypoxia is a prominent feature in the core region of HNSCC, which can reduce the effectiveness of radiotherapy, chemotherapy, and immunotherapy.[114] Additionally, CAFs play a crucial

role in the tumor microenvironment, and its high density is closely associated with local recurrence and poor prognosis in HNSCC.[156] To overcome these challenges, researchers are exploring the development of new bioinks, such as polyvinyl alcohol (PEG)-based bioinks which are modified by molecular engineering techniques and a 3D extrusion bioprinting composite bioink containing a reinforced decellularized ECM hydrogel to improve their biocompatibility and cell adhesion capabilities.[52,157] Additionally, the application of nanocomposite bioinks also shows the potential to enhance the properties of biomaterials, which are able to improve the mechanical strength, and bioactive of printed structures.[158] Given that diverse types of cells such as fibroblasts, mesenchymal stem cells, and CSCs,[159] as well as ECM molecules and signaling cues that can either inhibit or promote tumor growth, are present in the ECM, and it is of great significance to co-culture these cell lineages to minimize variability associated with using native tissues directly as an ECM source.[156,160] In future studies, optimizing the bioink formulation and printing process will be the key to enhancing bioprinting technology.[34]

Moreover, survival and functional maintenance of cells during printing remain challenging. For example, studies on bioprinting using modified hydrogel materials showed that CSCs were able to maintain high survival rates after printing and maintain their properties during *in vitro* culture.[161] In addition, for the printing of complex 3D structures, investigators are exploring new bioink formulations to improve cell survival and functions.[162] To overcome these challenges, researchers have adopted various strategies, such as the use of bioinks with excellent biocompatibility, combined with the printing of cells and biomaterials, to achieve better cell survival and functions.[163] In addition, the development of novel printing techniques, such as oil bath-based cell printing methods, has also been proposed to better protect the natural function of cells.[164] These advances open new possibilities for bioprinted complex tumor models and set the stage for future cancer research and therapeutic development.

Standardization is another important aspect of the clinical translation of bioprinted tumor models, as summarized in Table 6. Currently, there is a lack of uniform standards and specifications to guide the bioprinting process, including selection of materials, setting of printing parameters, and post-processing methods.[143] This lack of standardization may lead to inconsistent results between different laboratories, thereby affecting the reproducibility and reliability of the bioprinted models.[96] To overcome these challenges, researchers need to establish a comprehensive set of standardized processes to ensure the effectiveness and feasibility of bioprinting technology.[165] In addition, with the continuous progress of bioprinting technology, it is also particularly important to develop standardized bioinks and printing devices suitable for different applications.[166] Through the development of clear standards and norms, the clinical application of bioprinted tumor models will be smoother, ultimately promoting the development of personalized medicine.[167]

Finally, how to combine bioprinting technology with existing cancer treatments is also an important research direction. By integrating bioprinting technology and drug delivery systems, more accurate tumor treatment[3] can be achieved.[168] Advances in bioprinting technology have allowed researchers to build complex 3D tumor models that can better simulate the tumor microenvironment, thus providing a more realistic experimental platform for drug screening and treatment.[28] For example, the 3D-bioprinted tumor model that can effectively recapitulate the interactions between tumor cells and immune cells provides a possible avenue for the development of new immunotherapies.[169] In addition, bioprinting technology can also be combined with nanotechnology to develop more efficient drug

Table 6. Future recommendations of HNSCC treatments

Aspect		Requirements and directions
Requirements for standardization	Unified criteria	• Standardized processes for material selection, printing parameters, and post-processing methods
	Consistency	• Consistent results across laboratories to ensure data reproducibility and reliability
	Bioinks and devices	• Standardized bioinks and printing devices suitable for different applications
Future therapeutic orientation of HNSCC	Drug delivery	• Development of efficient targeted drug delivery systems using nanotechnology
	Personalized medicine	• Devising personalized treatment options to improve effectiveness and reduce side effects • Broader application prospects in cancer treatment
	Immunotherapy development	• Bioprinted models that simulate interactions between tumor cells and immune cells

delivery systems. These systems enable targeted drug delivery, reducing the effect of drugs on normal tissues, and improving therapeutic efficacy.[170] For example, drug carriers manufactured using bioprinting technology can achieve continuous release at the tumor site, thus increasing the local concentration of drugs and enhancing the antitumor effect.[171] By combining bioprinting with traditional oncology treatments, researchers are able to devise personalized treatment options to meet the needs of different patients. This approach can not only improve the effectiveness of treatment but also reduce side effects and provide better treatment options for cancer patients.[172] In the future, with the continuous development of bioprinting technology, its application prospects in cancer treatment will be broader.[173] Table 6 lists several future directions of HNSCC treatments.

Overall, the clinical transformation of bioprinted tumor models is promising. However, achieving this goal requires in-depth research and advancements in various aspects, including technology, standardization, and clinical application.

7. Conclusion

Bioprinting technology has shown substantial promise and significance in the advancement of tumor models for HNSCC. Bioprinting, by allowing for precise cellular arrangement and the reconstruction of tissue architecture, facilitates the simulation of the tumor microenvironment, recapitulates the complexity of the tumor tissue, and provides a more realistic biological model for drug screening and treatment response assessment.

These models play a vital role in enhancing our comprehension of tumor biology, screening new drugs, assessing therapeutic effectiveness, and identifying personalized treatment plans. Future research endeavors should aim to enhance the precision and efficiency of bioprinting technologies, with a particular emphasis on augmenting the diversity and functionality of cell types. Concurrently, the integration of insights derived from genomics and transcriptomics research is anticipated to empower bioprinted tumor models with the capability to more precisely replicate the distinctive features of patient-specific tumors, thereby facilitating advancements in personalized medical care. By integrating clinical data, bioprinting technology holds the promise of providing patients with more accurate treatment plans, reducing unnecessary side effects, and enhancing therapeutic outcomes.

However, despite the encouraging findings at present, model creation by means of bioprinting needs to be with caution. A lack of a uniform standard for cell type selection, printing parameters, and biomaterial selection may have limitative implications for the research results obtained. Therefore, future studies should aim to establish standardized processes to improve the reproducibility and reliability of experiments. Moreover, a repertoire of technical and biological challenges remains to be addressed urgently. For instance, in the process of bioprinting, the cell survival rate, tissue vascularization, and immunocompatibility are the key factors affecting the experimental results and clinical transformation. To surmount these challenges while broadening the application of bioprinting technologies, we need to integrate the strengths of bioengineering, materials science, and clinical medicine through a multidisciplinary collaboration.

Essentially, the study and implementation of bioprinting technology in the context of HNSCC not only uncovers innovative methods for developing tumor models but also plays a vital role in advancing the customization of treatment approaches. In the imminent era, bioprinting is anticipated to become progressively crucial in enhancing and optimizing treatment strategies for HNSCC. By synthesizing perspectives and breakthroughs from diverse research, this review contributes to driving the continuous evolution of this discipline, ultimately resulting in an elevation of the quality of life and living standards for patients.

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Conflict of interest

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