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Article ID: IJB026360385

Citation: Wu W, Yuan J, You R, *et al.* Three-dimensional bioprinting in oral and maxillofacial tumor treatment and reconstruction. *Int J Bioprint.* 2026. doi: 10.36922/IJB026360385

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Three-dimensional bioprinting in oral and maxillofacial tumor treatment and reconstruction

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Citation: Wu W, Yuan J, You R, *et al.* Three-dimensional bioprinting in oral and maxillofacial tumor treatment and reconstruction. *Int J Bioprint*. 2026. doi: 10.36922/IJB026360385

Received: August 31, 2026

Revised: September 20, 2026

Accepted: September 24, 2026

Published online: September 24, 2026

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Abstract

Treatment for oral maxillofacial cancer constitutes a highly specialized discipline encompassing tumor diagnosis, therapeutic management as well as the regeneration of oral cavity and related maxillofacial structure. In recent years, rapid advances in three-dimensional (3D) bioprinting technologies have profoundly transformed this field, enabling the development of innovative diagnostic and therapeutic equipment. This review primarily discusses the comprehensive and novel 3D bioprinting applications for the treatment of oral and maxillofacial neoplasms. It initially introduces the relevant steps, techniques, and materials to demonstrate the unique role of 3D bioprinting. Furthermore, this review marks its applications in treatment plans, mainly pointing out the use of 3D-printed clinical tools like preoperative biomodels, intraoperative surgical instruments, and postoperative reconstruction scaffolds, as well as other therapeutic tools like intraoral stents for radiotherapy and drug delivery systems for medication. Based on these contents, this review then not only reveals challenges of 3D bioprinting clinical therapies, but also proposes their latest progressions and potential directions, which can significantly improve the research of efficacy, precision, and prognosis in the field of malignant oral-maxillofacial tumors.

Keywords: 3D bioprinting; 3D printing; Oral and maxillofacial tumors; Tissue engineering; Maxillofacial reconstruction; Drug delivery

1. Introduction

Oral and maxillofacial tumors are among the most common malignancies worldwide and occur more frequently in older adults than in younger individuals. In addition to adverse effects of the cancer itself, various therapies, including surgery, radiotherapy, chemotherapy, and combined therapies, would all compromise both the function and aesthetics of the oral and maxillofacial region. These undesirable oral and maxillofacial alterations are mainly defects of hard tissues like bone and dentition, damage of soft tissues, and disruption of muscle attachment points along with muscle imbalance as well as significant facial deformities ^[1].

Over the past two decades, advances in biomedical engineering have established three-dimensional (3D) bioprinting as a transformative strategy for both therapeutic development and precise tissue reconstruction ^[2]. Its ability to precisely regulate scaffold porosity, spatial cell distribution, and high-resolution cell deposition while maintaining relatively low manufacturing costs has positioned 3D bioprinting as one of the leading regenerative technologies ^[3-5]. The benefits mentioned above allow the production of complex, cell-rich 3D constructs that are extremely similar to the natural tissue microenvironments, thus overcoming the main drawbacks of conventional scaffold-based approaches ^[6]. Although 3D bioprinting generally refers to cell-laden printing, this review also covers closely related acellular 3D-printed constructs that play vital roles in oral and maxillofacial tumor management. In this review, these acellular applications are referred to as 3D printing rather than bioprinting. Thus, this combination facilitates the development of customized and patient-specific medical devices, anatomical biomodels, and bioprinted therapeutic platforms, collectively supporting more precise and personalized treatment paradigms ^[7].

In recent years, numerous reviews have outlined the clinical applications of 3D printing within tissue engineering, including its use in dentistry. However, few focus on the treatment and prognosis of oral and maxillofacial tumor management. This review accentuates 3D bioprinting applications in oral and maxillofacial neoplasms, generally introducing its specific technology, steps, and relevant biomaterials, thereby accentuating its function of surgical tools, customized implant as well as therapy. Based on the content, it subsequently mentions the potential challenges and outlook in this realm. Overall, this review is intended to offer a practical and comprehensive

reference for next-generation solutions in oral and maxillofacial tumor research and clinical translation.

Relevant literature was searched in PubMed, Web of Science, and Scopus from database inception to 2026 using combinations of terms related to “3D bioprinting,” “3D printing,” “oral and maxillofacial tumors,” “reconstruction,” “surgery,” “radiotherapy,” and “drug delivery”. Original studies and relevant reviews addressing 3D bioprinting in oral-maxillofacial tumor treatment and reconstruction were included. Additional studies were identified from the reference lists of relevant articles.

2. 3D bioprinting technology and steps

The capability of 3D bioprinting is to deposit biomaterials in a layer-by-layer and spatially programmable manner, enabling precise regulation of scaffold architecture and porosity, as well as controlled spatial organization of cells, bioactive molecules, and the local microenvironment [8,9]. These outstanding abilities strengthen the clinical translatability of 3D bioprinting in clinical research and regenerative medicine. This section provides an overview of the general workflow and major bioprinting technologies.

2.1 Steps of 3D bioprinting

Generally, 3D bioprinting is divided into four steps (**Fig. 1**) [10]. This workflow is broadly applicable to tissue engineering, although the specific procedures and parameters may vary according to the target tissue and intended clinical use.

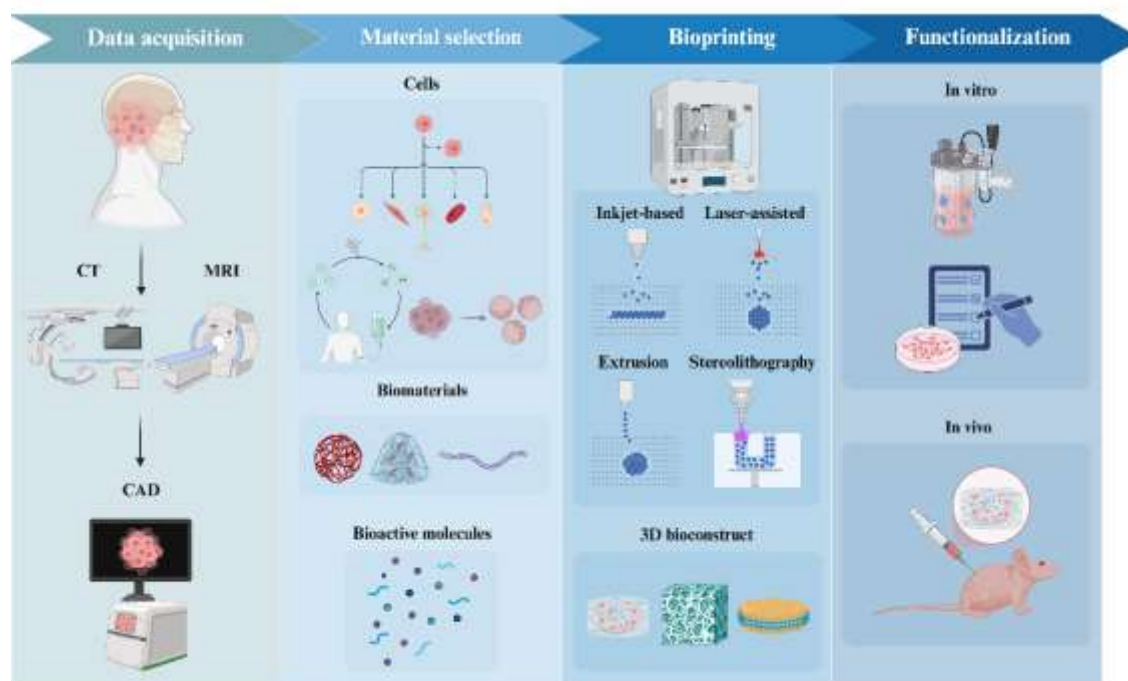


Figure 1. Steps of 3D bioprinting. Created in BioRender. Wu, W. (2026) <https://BioRender.com/ery4oto>

2.1.1 Data acquisition

In the first stage, images are acquired by advanced medical imaging modalities. The resulting datasets are subsequently converted into 3D digital models through computer-aided design (CAD)-based processing, followed by slicing into 2D horizontal slices. These models are typically stored in standardized digital formats, most commonly stereolithography (STL) files. According to different bioprinting approaches, these data are further processed into particles or filaments subsequently^[11,12].

2.1.2 Material selection

According to the specialized printed structures, bioinks including biomaterials, cells and bioactive molecules etc. should be carefully selected and combined. This step is crucial to guarantee properties of the final product, which may be required for biocompatibility, printability and mechanical stability.

2.1.3 Bioprinting

Following appropriate configuration of printing parameters, the 3D bioprinter applying different bioprinting methods uses the 2D particles or filaments as spatial guides to sequentially deposit biomaterials, living cells, and bioactive molecules according to the planned spatial arrangement, ultimately producing the desired 3D bioconstruct.

2.1.4 Functionalization

Following bioprinting, constructs undergo *in vitro* maturation or *in vivo* implantation to acquire biological functionality. For *in vitro* applications, bioprinted constructs are cultured under controlled conditions for disease modeling, drug screening, and biological evaluation. For *in vivo* applications, the constructs are implanted to support the survival of encapsulated cells and interactions with the host microenvironment.

2.2 Techniques of 3D bioprinting

A wide range of 3D bioprinting technologies are capable of fabricating biomimetic 3D architectures for applications in oral and maxillofacial neoplasms. In this section, several representative 3D bioprinting techniques are summarized below (**Fig. 2**)^[13].

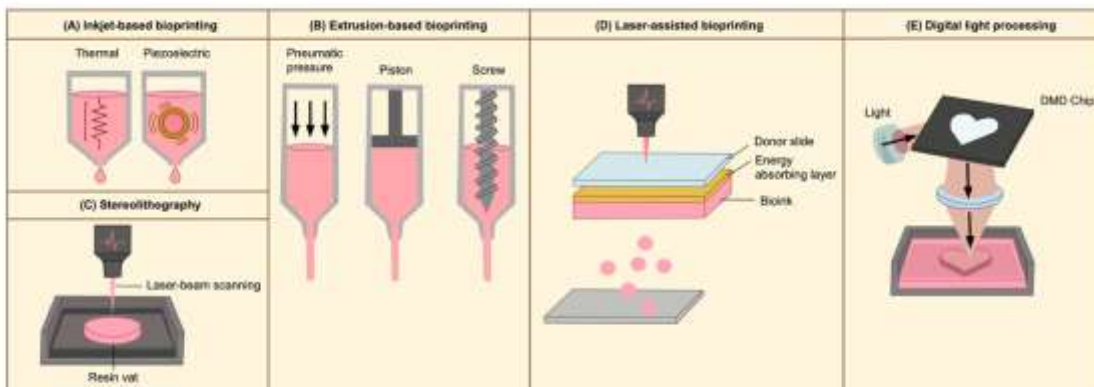


Figure 2. Techniques of 3D bioprinting. (A) Inkjet-based 3D bioprinting technology, (B) Extrusion-based 3D bioprinting technology (EBB), VAT photopolymerization technology (VPP): (C) stereolithography (SLA) and (D) Laser-assisted bioprinting technology (LAB), and (E) digital light processing (DLP).

2.2.1 Inkjet-based 3D bioprinting technology (IBB)

Inkjet-based 3D bioprinting encompasses both continuous and drop-on-demand operating modes, which manipulate bioinks containing living cells and bioactive constituents as spatially controlled microdroplets to construct tissues, scaffolds, or organ-mimetic structures.^[14] This approach is extremely simple to carry out, which allows for the creation of gradient patterns and exhibits high cell viability^[15].

2.2.2 Extrusion-based 3D bioprinting technology (EBB)

Extrusion-based 3D bioprinting utilizes the piston, screw, or pneumatic pressure to continuously extrude durable bioinks with high cell density and high viscosity through micron-scale nozzles^[16,17]. Filamentary bioink deposition can be stabilized on the printing platform through physical or chemical crosslinking^[15]. The ability to position cells precisely makes extrusion-based bioprinting well suited to producing complex cell-laden constructs^[18].

2.2.3 Laser-assisted bioprinting technology (LAB)

Laser-assisted bioprinting (LAB) is a touchless technique derived from laser-induced forward transfer (LIFT), which involves a pulsed laser source, a donor ribbon, and a receiving substrate^[19]. Transient high-pressure bubbles generated by laser irradiation transfer bioink droplets from the donor layer to the substrate^[20,21]. Because of its exceptional spatial accuracy and resolution, LAB supports deposition of highly concentrated cell suspensions or high viscosity bioinks, while avoiding significant mechanical stress^[19].

2.2.4 VAT photopolymerization technology (VPP)

The principle of vat photopolymerization (VPP) is light-induced polymerization, which uses light-sensitive resin systems that attain layer-by-layer spatial control through laser light sources or digital light projection^[22, 23]. Its main techniques are stereolithography (SLA) and digital light

processing (DLP) ^[24]. SLA provides incredibly high spatial accuracy and geometric precision for building sophisticated custom structures ^[25], while DLP supports small feature sizes and relatively high production throughput for applications requiring high geometric precision ^[24, 26].

2.2.5 Sacrificial stencil embedded printing technology

Sacrificial printing involves the fabrication of a removable mold, in which secondary functional materials are then filled ^[27]. Following selective removal of the sacrificial layer, interconnected cavities and microchannel networks would be formed within constructs. This technique facilitates recapitulating native physiological structures and functions, especially for the long-standing challenge of engineering vascular architectures of tissues and organs ^[28].

To demonstrate a comparison of different techniques, **Table 1** concludes their principles, advantages and limitations.

Table 1. Comparison of representative 3D bioprinting techniques.

Technique	Principle	Advantages	Limitations	Ref.
Inkjet-based bioprinting (IBB)	Spatially controlled microdroplet deposition by continuous or drop-on-demand printing	Low cost, scalability, simple operation, high cell viability	Limited bioink viscosity and cell concentration; nozzle clogging; relatively low resolution	14, 15
Extrusion-based bioprinting (EBB)	Continuous bioink extrusion through micron-scale nozzles using piston-, screw-, or pneumatic-driven systems	Broad material compatibility, high-viscosity& -cell-density bioinks, low cost	Relatively low resolution; shear stress, reduced cell viability, nozzle clogging	15-18
Laser-assisted bioprinting (LAB)	Laser-induced transfer of bioink droplets from a donor ribbon to a receiving substrate	High resolution, high-viscosity &-cell-density bioinks, low mechanical stress, high cell viability	High cost; complex operation; relatively low efficiency; potential contamination from donor materials	17-19
Vat photopolymerization (VPP)	Light-induced polymerization to undergo photoinitiated cross-linking & form polymer networks	High resolution & geometric fidelity, rapid layer-wise fabrication	Photocurable materials limitation, unstable cell activity, challenging multi-material printing	22-26
Sacrificial mold-assisted printing	Functional material deposition into a removable sacrificial mold to create internal cavities or channels	Interconnected cavities and vascular-like channels; complex internal structures; broad material compatibility	Incomplete removal may compromise construct integrity; compatibility between sacrificial and functional materials	27, 28

3. Biomaterials for 3D bioprinting in oral and maxillofacial tumors

The selection of biomaterials for 3D printing is influenced by several factors, including biocompatibility, appropriate mechanical characteristics, appropriate degradation rate, cell compatibility and sterilizing endurance. According to the criteria, there are approximately four types of biomaterials suitable for the treatment and reconstruction of oral and maxillofacial tumors. This section summarizes and compares these biomaterials.

3.1 Polymers

Polymeric scaffolds attract great interest in oral maxillofacial cancer treatment for their adjustable biodegradation kinetics, high porosity with controllable pore-size distributions, large surface-to-volume ratios, and adaptable mechanical performance ^[29-31]. They are generally classified as natural polymers or synthetic polymers.

Natural polymers include collagen, gelatin, chitosan, alginate, DNA, and RNA. Their excellent biocompatibility and biodegradability make them suitable for 3D printed drug delivery therapy and tissue regeneration after oral-maxillofacial tumors ^[32-35].

Synthetic polymers, including PCL, PGA, PLA, PLGA, PEO, PEG, PVA, and PU, are advantageous in compositional versatility, tunable physicochemical properties, controllable biodegradation and well-defined structural reproducibility ^[31, 34,36,37]. These materials can be used in drug delivery and maxillofacial constructs during oral and maxillofacial tumors treatment ^[38, 39]. Increasing evidence suggests that integrating natural and synthetic polymers for 3D printed constructs are likely to satisfy more clinical requirements ^[40].

3.2 Ceramic-Based Biomaterials

Ceramic-based biomaterials are of excellent mechanical strength, chemical stability, and favorable biocompatibility, which supports their application in osseous reconstruction post oral and maxillofacial tumor resection ^[41]. Common materials include calcium phosphate ceramics (HA, β -TCP, BCP), and BGs ^[42].

The compositional similarity between calcium phosphate ceramics and bone mineral has supported their widespread use in orthopedics and dental implantology. Notably, HA is frequently integrated with polymeric matrices to compensate for its inadequate fatigue resistance and relatively slow *in vivo* degradation^[15], while HA/ β -TCP ratio is modulated to alter their bioactivity and resorption behavior^[42].

Compared with calcium phosphate ceramics, BGs exhibit superior biodegradability and bioactivity. Additionally, it may facilitate angiogenic stimulation and normal bone formation through sustained release of silicon ions^[43].

Based on these properties, ceramic-based biomaterials are well suited for bone reconstruction and regeneration after oral maxillofacial neoplasm.

3.3 Metallic biomaterials

It has been reported that owing to their superior mechanical properties, metallic biomaterials, such as SS, titanium-based alloys, cobalt-based alloys, magnesium-based alloys, and SMAs, are generally regarded as more suitable for load-bearing reconstruction post oral-maxillofacial cancer^[44, 45].

Titanium alloys show excellent osteointegration and outstanding corrosion resistance, thereby establishing them as the current gold-standard materials for 3D-printed prostheses and implants in head and neck reconstruction^[46,47]. Compared with titanium, Co-Cr alloys possess enhanced fatigue strength and corrosion resistance, while NiTi-SMAs provide greater comfort, less bone resorption and more reinforcement of blood vessels. Notably, according to several studies^[47-49], additively manufactured NiTi highlights their potential advantages in mandibular reconstruction due to superior elastic properties and osteoconductivity^[44, 50].

Despite these advantages, metallic biomaterials may lead to cytotoxicity, chemical or electrical metal corrosion, and bone resorption, resulting in clinical failure^[44]. Surface modification can reduce these effects and improve osteointegration and antibacterial properties^[51, 52].

Thus, metallic biomaterials offer distinct advantages in oral-maxillofacial tumors reconstruction.

3.4 Cell-loaded bioinks

Bioinks mix biomaterials with living cells, which can recreate the in situ extracellular matrix support cell attachment, growth and differentiation for 3D bioprinting^[53,54]. During 3D bioprinting, bioinks play an essential role in the maintenance of cell viability, biocompatibility and mechanical performance. Various crosslinking or gelation methods convert the printed bioinks into a stable hydrogel or semi-solid construct^[53], which is subsequently cultured and evaluated^[55]. Additionally, cells enclosed within capsules should still maintain the ability to differentiate into specific phenotypes^[56].

Notably, while developing bioinks for the treatment and reconstruction of oral maxillofacial tumors, it is necessary to consider not only the biocompatibility, biodegradability, hydrophilicity, porousness and pH neutrality, but also the mechanical properties^[57-61].

To demonstrate a comparison of these biomaterials, **Table 2** concludes their category, advantages, disadvantages and representative applications.

Table 2. Biomaterials for the application of 3D bioprinting in oral maxillofacial cancer.

Material category	Detailed type	Name	Advantages	Disadvantages	Applications	Ref.
Polymers	Natural polymers	Collagen, gelatin, chitosan, alginate, DNA and RNA	Biocompatibility & biodegradability	Microbial contamination, restricted tunability, immunogenic responses, uncontrollable degradation behaviour, insufficient mechanical strength	Drug delivery system, maxillofacial bone regeneration	32
	Synthetic polymers	PCL, PGA, PLA, PLGA, PEO, PEG and PU	Tunable properties, endless forms, controllable biodegradation and established structures	Poor cell adhesion, low cell activity	Maxillofacial bone regeneration	31, 34, 36, 37
Ceramic-based biomaterials	Calcium phosphate ceramics	HA	Biocompatibility, osteoinductivity, cell viability	High brittleness, poor fatigue performance, slow degradation rate	Maxillofacial bone regeneration	41
		β -TCP	Mechanical stability, osteoconductivity, osteoinductivity,	High brittleness		41
		BCP	Mechanical stability, bioactivity, bioresorbability, osteoconductivity, osteoinductivity	High brittleness		15, 41
	Bioactive glasses	—	Mechanical stability, biodegradability, bioactivity	High brittleness		41, 43
Metallic biomaterials	—	Ti alloys	Biocompatibility, mechanical stability, resistance to corrosion	Toxicity from ions release and chemical reaction, oxidative corrosion, galvanic corrosion, stress shielding	Dentistry, TMJ replacement	44,46
		Co-Cr alloys	Superior fatigue strength, corrosion resistance		Maxillofacial bone regeneration	44,46
		Ni-Ti SMA	Featherweight, inertness, shape memory features		Load-bearing maxillofacial bone regeneration	44,49
Cell-loaded bioinks	Living cells	Oral stem cells	Biocompatibility, mechanical stability, cell viability, hydrophilicity, porosity, pH neutrality, biodegradability	—	Oral maxillofacial cancer treatment & regeneration	55, 57-61

4. Application of 3D bioprinting in oral-maxillofacial tumors

Associating biomaterials with proper 3D bioprinting technology is the initial step of the process of maxillofacial-oral neoplasm treatment, followed by the stage of choosing multiple helpful applications of various additive manufactures as aids for surgery, regeneration and customized therapy. This section presents applications of 3D bioprinting in the diagnosis, therapies and

prognosis for oral-maxillofacial carcinoma while some 3D-printed aid applications would also be mentioned for comprehensive elaboration of bioprinted applications (**Fig. 3**).

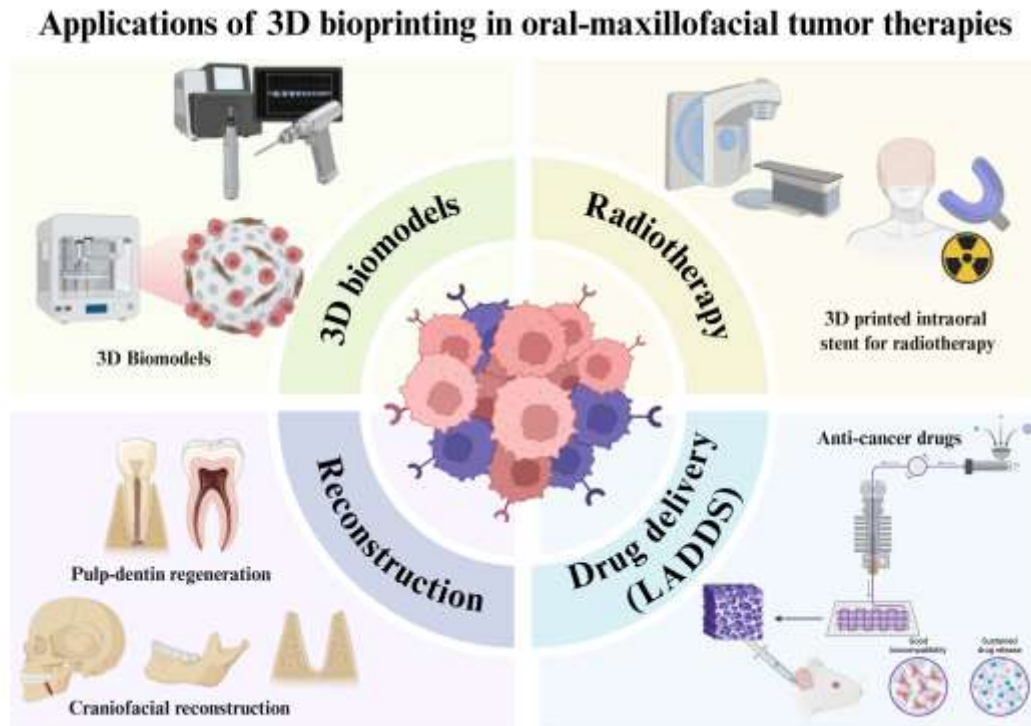


Figure 3. Applications of 3D bioprinting in oral-maxillofacial tumor therapies. Created in BioRender. Wu, W. (2026) <https://BioRender.com/7crdugy>

4.1 Application of 3D bioprinting in oral-maxillofacial tumor surgical therapies

For resectable oral and head and neck tumors, the objective is to approach safety and efficiency. Current literature identifies four principal clinical domains in which 3D printing has been extensively implemented: dental implant procedures, orthognathic surgeries, mandibular reconstruction via free fibula flaps, and midfacial repair ^[62]. For instance, 3D printing enables comprehensive preoperative planning and surgical simulation by providing patient-specific anatomical models, customized osteotomy and drilling guides, pre-contoured fixation plates, and personalized implants that ensure accurate implant positioning and screw orientation ^[63,64]. Thus, integrating 3D printing into routine surgical planning is a helpful way to reduce surgical time, increase safety and accuracy, as well as improve esthetic outcomes.

4.1.1 3D biomodels for oral-maxillofacial tumor surgeries

For oral-maxillofacial surgeries, 3D biomodels include patient-specific anatomical models and *in vitro* tumor models, which is absolutely beneficial for diagnosis, surgery of oral-maxillofacial tumors and postoperative care. Anatomical models involve the use of 3D printing to reproduce macroscopic anatomical structures based on the imaging data, while 3D-bioprinted tumor models enable the precise deposition of bioinks to create complex, tissue-like structures that mimic the *in vivo* tumor microenvironment [65-68].

Simple anatomical models are difficult to fully reproduce the spatial structure, intercellular interactions, hypoxic conditions, and heterogeneity of oral and maxillofacial cancers. For OSCC, this limitation is particularly evident, as its microenvironment is composed of tumor cells, stromal cells, immune cells, vascular components, signaling molecules, and extracellular matrix with heterogeneity [69, 70]. By controlling the deposition of cells and biomaterials, 3D bioprinting can regulate matrix composition, stiffness, and spatial cell distribution, thereby constructing complex, multicellular, and highly reproducible tumor models that more faithfully recapitulate *in vivo* conditions [55,71]. As to cell selection, patient-derived OSCC cells for 3D bioprinting can better retain the genetic and phenotypic features of the tumors, providing more knowledge for surgeries [72]. In another research, Klangprapan et al.[73] reported a magnetic 3D bioprinting (M3DB) protocol that allowed rapid formation of scaffold-free salivary gland (SG) mucoepidermoid carcinoma (MEC) tumoroid, which closely simulated features of native SG MEC.

These 3D-bioprinted *in vitro* tumor models can complement 3D printed patient-specific anatomical models which could provide more accurate diagnostic evaluation and develop precise surgical strategies. Before operation, patient-specific 3D-printed models depict detailed anatomical structures and help to locate key elements such as major blood vessels and nerves. This capability is particularly important because oral and maxillofacial tumors often distort the adjacent vessels or even recruit new blood vessels, thus increasing the risk of accidental bleeding during resection. The incorporation of 3D-printed models with virtual soft-tissue simulation has been shown to reduce this risk by more precise surgical planning. Parr *et al.* [74] stood out on how presurgical models decreased operative risk factors. Specifically, it is achieved by shortening surgical duration, reducing unexpected anatomical variations, and enhancing control over preoperative workflow.

Thus, the finding does strongly support the conclusion that 3D biomodels are essential tools to avoid accidental bleeding during operation. What's more, 3D biomodels also contribute to postoperative management. Irace *et al.* ^[75] introduced a method for postoperative management, where resected oral and oropharyngeal tumors were photographed and reconstructed using 3DP. Through accurate imaging of the tumor margins and spatial location, this method supports more improved and specific postoperative management. In addition, Zhou and colleagues ^[76] extended the application of GelMA-Col-hyaluronic acid to 3D bioprinting for fabricating *in vitro* tumor models that accurately emulate the native extracellular matrix, providing a potentially more efficient anti-cancer drug screening tool post surgeries.

Notably, if integrated with a static 3DP surgical guidance system, the biomodels would be fabricated more precisely. For instance, it was reported that a facial tumor (fibrous dysplasia) was accurately sculpted with a selective laser sintering (SLS)–printed drill guide, which translates a virtual 3D surgical plan directly to the operative field, thereby serving as a critical interface between digital planning and the physical biomodel ^[77]. Years later, Tian *et al.* ^[78] reported that the drill guides manufactured by SLA can precisely define drilling position, angulation, and depth, allowing key parameters from preoperative simulations to be reliably transferred to the intraoperative setting and effectively bridging the gap between planned and executed procedures. Further, García-Sevilla *et al.* ^[79] assessed surgical accuracy by calculating the spatial deviation between points collected along tumor margins defined by a 3D-printed navigation system and the actual tumor boundaries. In another research, Al-Harbi and Sun ^[80] proposed that with the aid of stereolithographic guides, the accuracy and effect planned before the operation and the actual outcomes were almost exactly matched in spatial position and axial orientation. With these improvements and advancements, it is promising to utilize the 3DP guidance system for developing more accurate oral-maxillofacial tumor biomodels.

In sum, 3D-printed biomodels are not only helpful for oral-maxillofacial cancer diagnosis but also beneficial for preventing surgical accidents (**Fig. 4**).

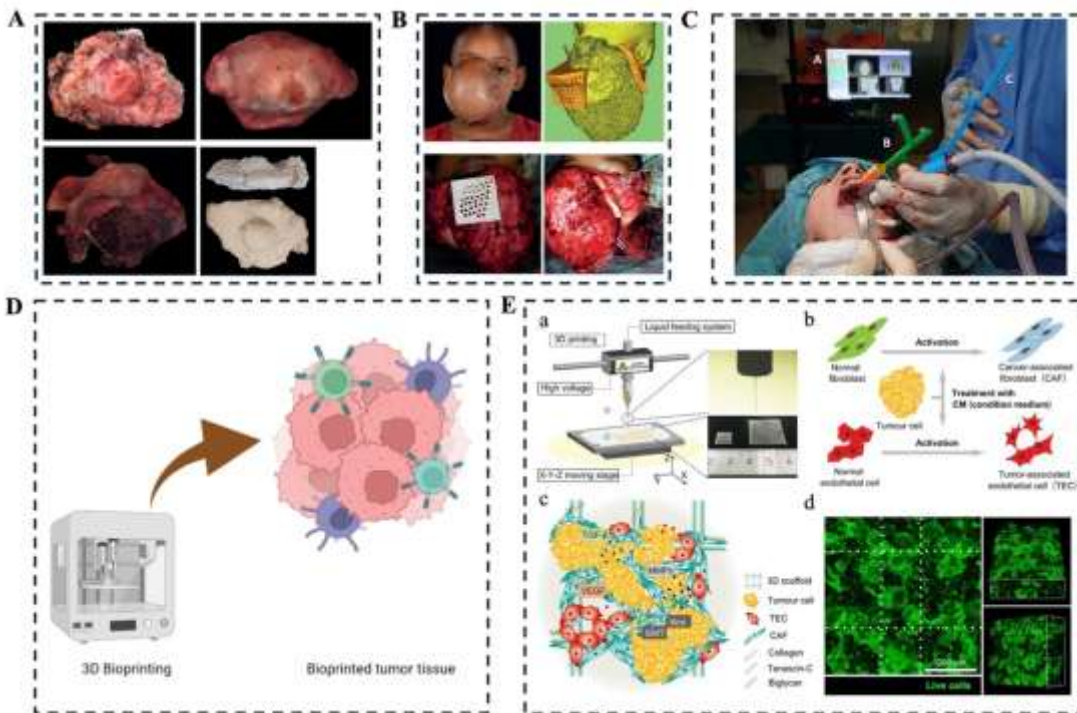


Figure 4. 3D biomodels for oral maxillofacial tumor surgeries: (A) Examples of 3D biomodels for oral cancer. Reproduced from ref.75 with permission. Copyright 2021, MDPI. (B, C) 3D printed tools for accurately imaging the tumor: (B) SLS-fabricated drill guide for accurately sculpt the tumor (Reproduced from ref.77 with permission. Copyright 2015, Springer Nature.) and (C) 3D printed navigation system for locating the tumor margins. Reproduced from ref.79 with permission. Copyright 2022, All authors. (D, E) The fabrication process of 3D biomodels: (D) The illustration of 3D bioprinting oral-maxillofacial tumor model (Reproduced from ref.55 with permission. Copyright 2023, Elsevier.) and (E): The fabrication and characterization of 3D bioprinted collagen-PCL tumor scaffolds incorporating stromal and tumor cells for analyzing cell proliferation, adhesion, stemness, and heterogeneity. Reproduced from ref.69 with permission. Copyright 2020, Theranostics.

4.1.2 Customized scaffold for reconstruction after oral-maxillofacial tumor surgeries

Oral-maxillofacial cancer resection may significantly impair tissue function and appearance, reducing life quality. Given this postoperative defect, the role of 3D customized scaffolds is in the center of reconstruction, which includes shaping and outlining the craniofacial and dental rehabilitation aligned with surgical reconstruction alternatives ^[1].

Regarding craniofacial bone reconstruction, numerous studies have reported the advance of 3D bioprinted scaffolds in this realm recently (**Fig. 5**). The first breakthrough is that 3D bioprinting allows for tailoring the scaffold's architecture that greatly resembles native craniofacial bone tissue microenvironments. This technology enables the seamless integration of bioactive substances,

growth factors, minute molecules, or their blending within the scaffold structures, thereby markedly boosting its regenerative potential ^[81]. Multi-material 3D printed scaffolds that are modified with osteogenic and angiogenic growth factors, such as BMP-2 and VEGF, promote an impressive amount of bone formation with vascularization ^[82]. For instance, Cao *et al.* ^[83] designed 3D bioprinted scaffolds made of PLGA/TCP and TCP, which were either coated with rhBMP-2, or left untreated. The post-surgery analyses showed enhanced neovascularization in implanted TCP-BMP scaffolds, with remarkable recruitment and differentiation of MSCs contributing to better reconstruction of mandibular bone. Nevertheless, despite these encouraging regenerative outcomes, the clinical application of rhBMP-2 in oral-maxillofacial oncologic reconstruction remains controversial. The biological effects of rhBMP-2 may be dose-dependent, and high local concentrations have been associated with concerns regarding ectopic bone formation and potential tumor-promoting effects in certain malignancies. Therefore, careful safety evaluation remains essential before its routine clinical application in tumor reconstruction. Another work led by Lee *et al.* ^[84] showed that PCL/TCP/bdECM scaffolds combined with ADSCs in a canine mandibular model, resulting in a pronounced enhancement of osteoinductive and osteoconductive performance, tissue regeneration and healing process. Apart from the regeneration of craniofacial bone, 3D printing also supports the reconstruction of the temporomandibular joint (TMJ). Abramowicz *et al.* ^[85] utilized 3D printing to fabricate a PCL scaffold, which was subsequently treated with BMP-2 and engineered with vascular networks to facilitate the regeneration of functional TMJ tissue. After implantation into the temporalis muscles of three minipigs, the scaffold demonstrated successful in situ vascularization within a six-week postoperative period. After rotation to the condyle defect site, the scaffold showed new bone formation with blood vessels. Thus, these studies show the potential of customized 3D printed scaffolds in promoting natural craniofacial bone and TMJ regeneration as well as improving functional restoration after oral-maxillofacial neoplasm operations.

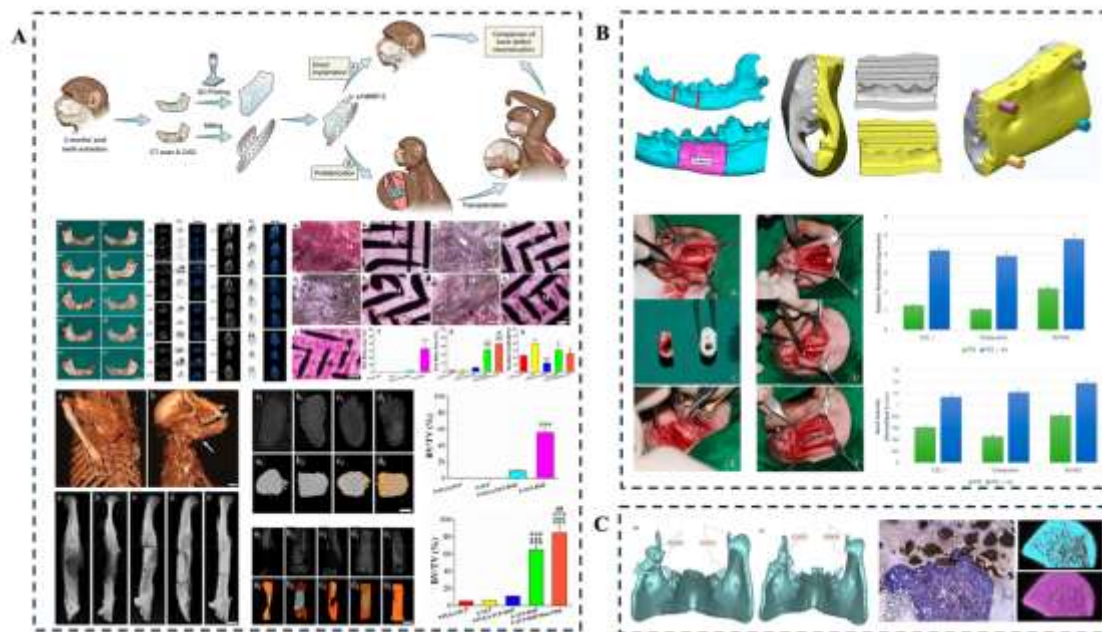


Figure 5. Customized scaffold for craniofacial bone reconstruction after oral-maxillofacial tumor surgeries: (A) 3D-printed β -TCP scaffolds with rhBMP-2 coating effectively repaired large mandibular defects in primates, promoting bone regeneration and vascularization compared with PLGA/TCP scaffolds or direct implantation. Reproduced from ref.83 with permission. Copyright 2021, American Chemical Society. (B) In a beagle mandibular reconstruction model, 3D-printed PCL/TCP scaffolds coated with bDECm and injected with ADSC aggregates enhanced ossification within scaffold pores and surrounding tissues, showing increased osteogenic marker expression without immune rejection. Reproduced from ref.84 with permission. Copyright 2021, MDPI. (C) A proof-of-principle porcine model was developed for pediatric TMJ mandibular condyle reconstruction using a load-bearing, customized 3D-printed scaffold coated with BMP-2 and implanted within a pedicled temporal flap. Reproduced from ref.85 with permission. Copyright 2021, Elsevier.

Oral and maxillofacial tumors and their treatment may also compromise dentoalveolar tissues, including teeth, alveolar bone, periodontal structures, and the pulp–dentin complex. Tumor resection can directly remove tooth-bearing bone and adjacent dental tissues, whereas radiotherapy may further impair vascularity, wound healing, and the long-term maintenance of oral structures. Consequently, dental rehabilitation becomes an important part of functional reconstruction following oral-maxillofacial tumor surgery. 3D bioprinting engineers dental tissues through the spatial integration of living cells and extracellular matrix–mimicking materials for dental pulp and tooth germs exclusively^[86], while to date, there is only a limited range of polymeric biomaterials including collagen, GelMA, and PLA combined with 3D printing are targeted at dental regeneration (**Fig. 6**)^[15,87-89]. A study has proposed that scaffolds composed of polycaprolactone combined with either bioglass or hyaluronic acid would show remarkable promise for pulp-dentin

regeneration by supporting the attachment of BMSCs and spurring their odontogenic differentiation^[15]. This report gives a potential insight into the pulp-dentin regeneration after oral cancer resection. For instance, Jiang *et al.*^[87] employed low-temperature deposition 3D printing to construct type I CSF scaffolds with varying pore sizes loaded with human dental pulp cells (HDPCs), showing increased adhesion and proliferation of HDPC multilayers. Thus, this bioconstruct highlights the promise for dentin-pulp complex regeneration. In another research, Chen *et al.*^[88] have reported an experiment where DPSCs seeded onto 3D-printed HA/PLA scaffolds and subsequently implanted into the dogs' mandibular defect sites exhibited pronounced mineralization after a nine-month implantation period. Similarly, Feng *et al.*^[89] succeeded in conducting biomimetic mineralization and odontogenic differentiation of DPSCs cultured on 3D-printed PLA scaffolds. Recent studies have provided further preclinical evidence supporting pulp-dentin regeneration. For instance, Zhou *et al.*^[90] developed GelMA-Dextran-based bioprinted constructs that supported the formation of tissue with dental pulp characteristics in a mouse subcutaneous model. Zhu *et al.*^[91] promoted the in-situ formation of dental pulp stem cell spheroids within 3D bioprinted hydrogels and observed dentin-like structures and vascularization after implantation. More recently, Liu *et al.*^[92] demonstrated enhanced microvascular formation and pulp-like tissue regeneration using prevascularized 3D bioprinted hydrogels combined with human root segments in nude mice. Collectively, these studies support the potential in the realm of pulp and dental regeneration within 3D printing after oral neoplasm operation. However, their ability to restore a fully functional pulp-dentin complex in clinical settings, particularly following oral-maxillofacial tumor resection, requires further validation. As in the context of oral and maxillofacial neoplasms, regeneration involves more than morphological reconstruction of the resected tissues. Successful regeneration also requires adequate vascularization, functional integration with the surrounding tissues, and long-term restoration of oral function. Moreover, regenerative strategies following tumor treatment must account for oncologic safety and the compromised local tissue environment caused by surgery and radiotherapy. These considerations distinguish post-tumor regeneration from conventional tissue regeneration and remain important challenges for the clinical translation of 3D bioprinting.

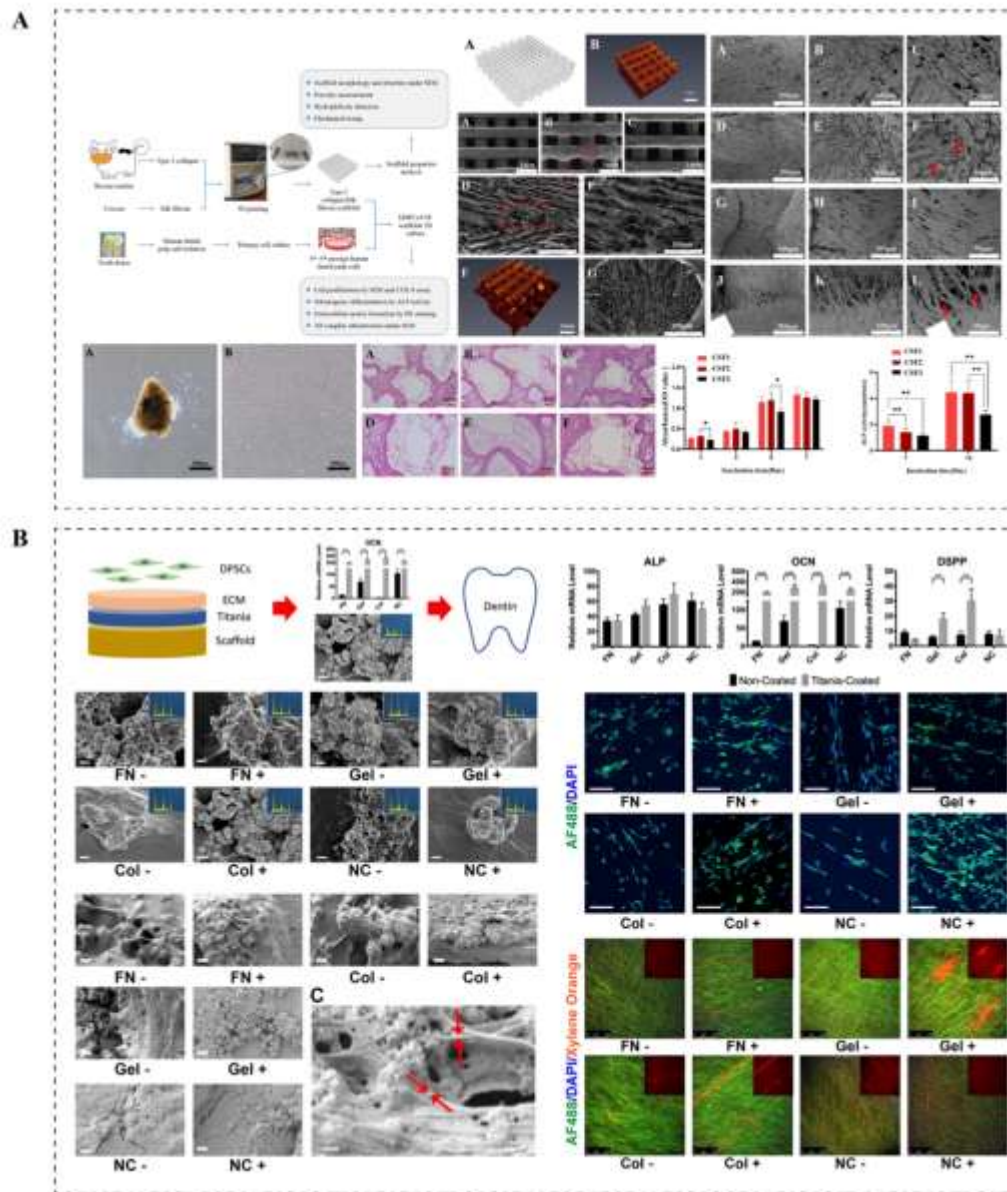


Figure 6. 3D bioprinting for dentoalveolar tissue reconstruction after oral-maxillofacial tumor surgery: (A) 3D-printed collagen/silk fibroin scaffolds with varying pore sizes enhanced adhesion, proliferation, and ALP activity of HDPCs, supporting dentin–pulp complex regeneration. Reproduced from ref.87 with permission. Copyright 2021, Authors. (B) 3D-printed PLA scaffolds coated with titania by atomic layer deposition (ALD) promoted biomineralization and odontogenic differentiation of dental pulp stem cells. Reproduced from ref.89 with permission. Copyright 2021, American Chemical Society.

In sum, customized 3D printed scaffolds are promising tools for reconstruction after oral-maxillofacial tumor resection.

4.2 Application of 3D bioprinting in other oral-maxillofacial tumor therapies

Medical treatment is one of the main means of oral-maxillofacial tumor treatment, including radiotherapy and drug delivery. The integration of 3D printing with medical therapy can improve the treatment techniques and minimize side effects.

4.2.1 3D printed intraoral stents for oral-maxillofacial cancer radiotherapy

Radiotherapy remains a cornerstone in the management of head and neck malignancies; however, its clinical efficacy is often accompanied by acute and long-term adverse effects on surrounding healthy tissues. To mitigate these complications, 3D-printed intraoral stents have been developed to modulate radiation delivery and spatially confine dose exposure to designated target regions (**Fig. 7**). Brandão *et al.* ^[93] reported that the utilization of intraoral stents significantly reduced radiotherapy-induced oral toxicities, including oral mucositis, trismus, xerostomia, and unnecessary radiation exposure to healthy structures. Specifically, Bruno *et al.* ^[94] reported a marked reduction in radiation dose to non-target tissues, particularly to antagonistic structures, when using 3D-printed oral stents. Similarly, Hong *et al.* ^[95] reported a 3D printed patient-specific semi-customized tongue displacement device (SCTDD), which achieved a significant reduction in radiation dose to the tongue compared with conventional standard mouthpieces in maxillofacial radiation therapy. In another research, Cleland *et al.* ^[96] utilized a solid head phantom to show that polylactic acid (PLA)-based 3D-printed stents provided tissue displacement and dose reduction comparable to those achieved using conventional wax stents. Further, Mota *et al.* ^[97] proposed that 3D-printed intraoral stents were shown to be as effective as commercially available semi-customized and manually fabricated standard stents, with reproducible positioning and comparable soft tissue displacement, particularly of the tongue. Recent research have further studied the clinical applications of these devices. For example, Tino *et al.* ^[98] reported successful fabrication and good patient tolerance of customized 3D-printed stents for oropharyngeal cancer patients in the lead-in phase of a multicenter trial. In a 12-patient comparison, Li *et al.* ^[99] found broadly similar homogeneity index and conformity index of the target areas for head and neck malignancies, as well as the dose differences to the organs at risk between 3D-printed and manually fabricated

stents, with shorter fabrication time and higher patient satisfaction for the 3D printed devices. Collectively, these studies indicate that 3D-printed intraoral stents demonstrated excellent performance in reproducibility and adaptation while having great potential in protecting healthy tissues from maxillofacial radiotherapy.

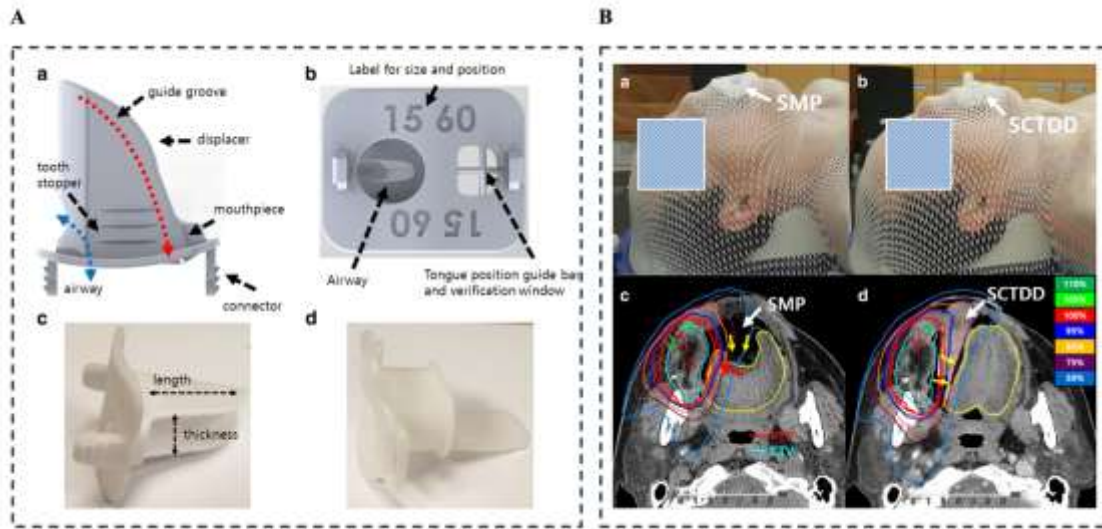


Figure 7. 3D printed intraoral stents for oral-maxillofacial cancer radiotherapy. (A, B) Design and clinical evaluation of SCTDD compared with SMP for cancer radiotherapy: (A) The fabrication of 3D printed SCTDD by biocompatible material, comparing with the commercially available SMP. (B) Patient setup and axial isodose distributions showing that the SCTDD effectively displaced the tongue from the high-dose region near the target, whereas the SMP only depressed the tongue without contralateral displacement. Reproduced from ref.95 with permission. Copyright 2019, The authors.

4.2.2 3D printed long-acting drug delivery system (LADDs) for oral-maxillofacial tumor

Systemic administration of chemotherapeutic agents via oral or intravenous routes remains a primary treatment modality for oral and maxillofacial malignancies (**Fig. 8**)^[100-102]. However, the requirement for high drug dosages frequently leads to severe systemic toxicity and associated adverse effects. In recent decades, accumulating evidence has highlighted the potential of 3D printing technologies for LADDs, enabling site-specific chemotherapy with reduced systemic exposure^[101,103]. For instance, Yang *et al.*^[103] developed an implantable 3D-printed PLGA scaffold for the localized immobilization and sustained release of 5-fluorouracil and NVP-BE235. This strategy significantly reduced the required drug dosage, maintained therapeutic concentrations in proximity to the tumor over extended periods, and minimized off-target drug exposure to healthy tissues. This 3DP LADDs is specialized for breast cancer, however, it offers

great insight into the extensive 3D bioprinted application on oral maxillofacial cancer in terms of the fulfilment of long-term drug release, single-implant administration, and reduced treatment frequency. One year later, Li *et al.* ^[104] reported using 3D printing technology to fabricate curcumin-loaded polycaprolactone (PCL) filaments with diverse geometries using 3D printing, resulting in flexible and biodegradable drug-eluting scaffolds for localized intracranial therapy of glioblastoma multiforme. These findings suggest the therapeutic potential of implantable drug delivery platforms in suppressing tumor recurrence, which is a potential application in oral-maxillofacial tumors. In another research, Wang *et al.* ^[105] proposed a personalized, biodegradable 3D-printed implant capable of controlled drug release for local chemotherapy of osteosarcoma. This implant achieved sustained drug release at the tumor site for up to 12 weeks, thereby enhancing therapeutic efficacy and further supporting its potential application in maxillofacial osteosarcoma treatment. These studies summarize the conclusion that the use of 3DP LADDs can improve drug release efficiency and significantly inhibit the recurrence of malignant oral and maxillofacial tumors.

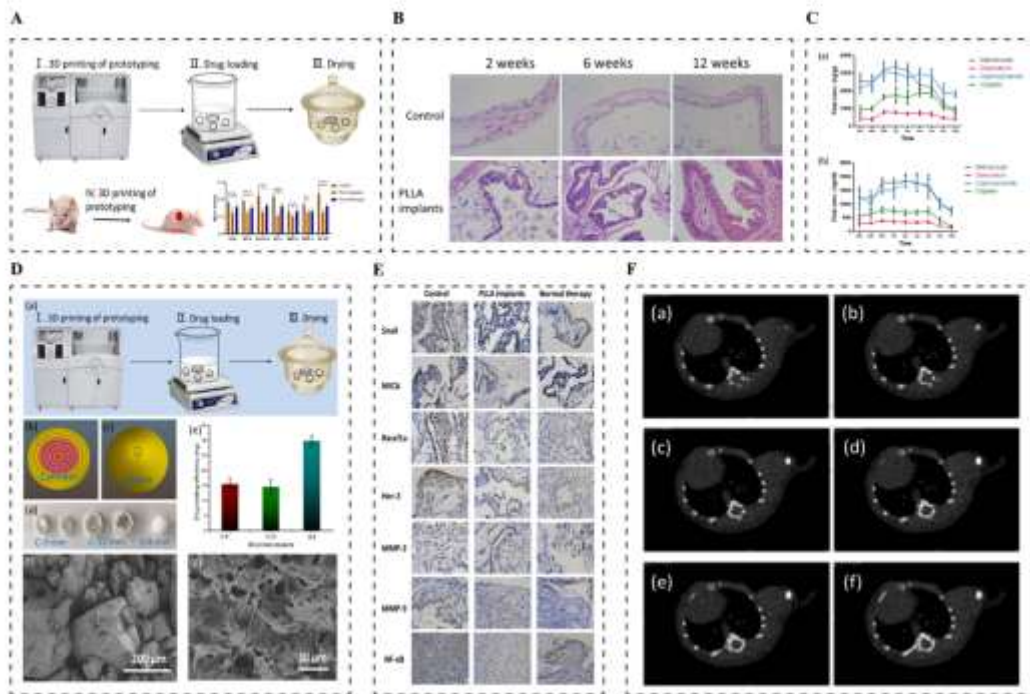


Figure 8. 3D printed LADDs for oral-maxillofacial cancer treatment. (A) Development of a 3D printing technique for personalized PLLA drug-loaded implants enabling sustained local chemotherapy and improved anti-osteosarcoma efficacy, (B) Histological evaluation showing mild inflammation and good biocompatibility around the PLLA implant sites in rabbits, (C) Drug concentration analysis in local lesion tissue and systemic blood indicating controlled local

release with reduced systemic exposure, (D) Design and characterization of 3D-printed PLLA implants with tunable geometry, drug-loading efficiency, and porous microstructure, (E) Immunohistochemical analysis demonstrating that PLLA drug-loaded implants achieved effective tumor inhibition with reduced systemic toxicity compared to conventional chemotherapy, and (F) Micro-CT images confirming no tumor recurrence and long-term safety after local chemotherapy using PLLA implants. Reproduced from ref.105 with permission. Copyright 2020, The authors.

More generally, integration of 3D bioprinting into radiotherapy and drug delivery systems in oral and maxillofacial cancers provides a linear approach to treatment trends, supporting the establishment of personalized oncological treatment systems. Nonetheless, further research is required in order to fully realize and perfect the technology prior to its full application.

Table 3 provides an intuitive summary of the application of 3D bioprinting in oral and maxillofacial tumors, highlighting the wide range and future potential of this technique.

Table 3. The application of 3D bioprinting in oral-maxillofacial carcinoma.

3D bioprinting strategies	Biomaterials	Cell types / Growth factors/ Drugs/ Microbes	Construct	Function	Evidence base level	Ref.
3D bioprinting						
3D bioprinting	Bioinks (tumour cells and ECM)	Oral-maxillofacial cancer cells	3D bioprinted model	Simulating tumor microenvironment for diagnosis, surgeries and postoperative care	<i>In vitro</i> , clinical research	55, 75, 76
Magnetic 3D bioprinting	—	Salivary gland MEC cells	Scaffold-free MEC tumoroid	Recapitulating salivary gland MEC characteristics for tumor modeling	<i>In vitro</i>	73
3D bioprinting	PLGA/TCP	rhBMP-2	PLGA/TCP craniofacial scaffold	Mandibular bone regeneration	<i>In vivo</i>	83
3D bioprinting	PCL/TCP	bdECM, ADSCs, BMSCs	PCL/TCP craniofacial scaffold	Craniofacial bone regeneration	<i>In vivo</i>	84
Laser-assisted bioprinting	PCL	BMP-2	PCL TMJ scaffold	Functional TMJ regeneration	<i>In vivo</i>	85
3D bioprinting	PCL/BG, PCL/ hyaluronic acid	BMSCs	PCL/BG pulp-dentin scaffold PCL/ hyaluronic acid pulp-dentin scaffold	Pulp-dentin complex regeneration	<i>In vitro</i> , <i>in vivo</i>	15
Low-temperature deposition 3D bioprinting	Type I CSF	HDPCs	Type I CSF pulp-dentin scaffold	Pulp-dentin complex regeneration	<i>In vitro</i>	87
3D bioprinting	HA/ PLA	Dental pulp stem cells	HA/PLA tooth scaffold	Tooth regeneration, pulp regeneration	<i>In vivo</i>	88
3D bioprinting	PLA	Dental pulp stem cells	PLA tooth scaffold	Tooth regeneration	<i>In vitro</i>	89
DLP-based 3D bioprinting	GelMA/Dextran	DPSCs	Dental pulp guidance construct	Pulp–dentin and vascular regeneration	<i>In vitro</i> , <i>in vivo</i>	90

DLP-based 3D bioprinting	GelMA/Dextran	DPSCs	Stem cell spheroid-laden hydrogel construct	Dentin and vascular regeneration	<i>In vitro, in vivo</i>	91
3D bioprinting	GelMA	SHEDs, HUVECs	Prevascularized hydrogel construct	Vascularized dental pulp regeneration	<i>In vitro, in vivo</i>	92
3D printing	—	—	Customized oral stents	Oral tissue positioning and protection during radiotherapy	Clinical research	98,99
3D bioprinting	Poly-lactic-co-glycolic acid	5-fluorouracil, NVP-BEZ235	Poly-lactic-co-glycolic acid implanted LADDS	Long-term and controlled drug release	<i>In vivo</i>	103
3D bioprinting	PCL	Curcumin	Curcumin-loaded PCL LADDS	Localised LADDS for intracranial therapy of Glioblastoma Multiforme, controlling the recurrence of malignant cancers	<i>In vitro</i>	104
3D bioprinting	PLLA	Anticarcinogen	PLLA implanted LADDS	Localised LADDS for local chemotherapy of osteosarcoma,	<i>In vivo</i>	105
3D printing						
SLS	—	—	SLS drill guides	Sculpting facial tumor for accurate biomodels	Clinical research	77
SLA	—	—	SLA drill guides	Guide for the insertion position, orientation, and penetration depth of the operation	Clinical research	78, 80
3D printing	PLA	—	PLA oral stents	Healthy tissue protection from maxillofacial radiotherapy.	Clinical research	93-95, 97

5. Challenges and Outlook

3D printing technologies have increasingly transformed the management of oral and maxillofacial neoplasms, substantially improving treatment accuracy. Despite these advances, several technical and translational limitations continue to constrain the broader implementation of 3D printing in surgical procedures and other therapeutic methods. Accordingly, prospective directions are also proposed in this part for further refinement and exploration.

5.1 Challenges and prospects for 3DP surgical therapies

Despite the considerable promise of 3DP-assisted surgical approaches, several limitations must be acknowledged. As with any surgical technology, equipment-related failures should also be considered, and appropriate contingency strategies should be established if 3DP is to be routinely integrated into patient care. Besides, the range of clinically approved printable materials remains limited, and further optimization of their physicochemical and biological properties is required. Notably, long-term *in vivo* stability and performance of implanted biomaterials have not been

sufficiently validated in most existing studies. Future studies should therefore focus on the rational design of internal architectures and advanced surface modification strategies, together with innovative material exploitation^[81]. Additionally, current methods that rely on digital photography for 3D reconstruction may incompletely capture tissue geometry, particularly for surfaces in contact with underlying supports. Specifically, in some cases specimens cannot be fully rotated during imaging due to the risk of structural deformation, which can compromise image registration and subsequent 3D model accuracy. To overcome this limitation, the development of dedicated imaging fixtures or holders designed to allow full exposure of the sample surface has been suggested as a feasible solution^[71,75].

Beyond these specific technical constraints, several promising directions may further extend the role of 3D printing in the management of oral and maxillofacial neoplasms. Alongside continued progress in regenerative medicine, the incorporation of pro-regenerative and pro-angiogenic cues into bioprinted constructs underscores the potential of 3D bioprinting as an effective approach for the fabrication of functional tissues, including bone, cartilage, and oral mucosa. In parallel, drug delivery systems can be incorporated into 3D-printed surgical templates to enable localized administration of therapeutic agents at the operative site, such as antimicrobials for infection prevention and analgesics for postoperative pain management. This strategy may improve surgical outcomes while minimizing systemic adverse effects^[81]. Therefore, large-scale prospective studies remain necessary to rigorously evaluate the clinical utility of 3D printing in oral and maxillofacial surgical procedures and to establish evidence-based guidelines for its optimal implementation in oral and maxillofacial cancer treatment.

5.2 Challenges and prospects for other 3DP therapies

For radiotherapy assisted by 3D-printed intraoral stents, treatment-related oral toxicities remain a critical factor that may limit therapeutic efficacy. While most existing studies primarily focus on the preventive role of intraoral stents during irradiation^[93,106,107], the current research lacks controlled and randomized studies to evaluate both short- and long-term outcomes. In particular, systematic analyses correlating oral toxicities with irradiation sites and radiotherapy modalities are still insufficient^[97]. Therefore, future research should accentuate more controlled and randomized

studies to generate robust evidence for identifying optimal 3D-printed stent designs, as well as to comprehensively assess their safety, efficacy, and impact on acute and chronic oral toxicities.

For 3D bioprinted LADDs, growing evidence indicates that it can markedly improve therapeutic efficacy in cancer treatment by enhancing drug bioavailability, reducing systemic adverse effects, enabling localized or targeted drug administration, and improving patient compliance ^[101,108,109]. However, a major unresolved issue remains the rising cost of bioprintable biomaterials, with the limited understanding and restricted availability of excipients that are compatible with both 3D bioprinting processes and microneedle-based platforms. Therefore, prospective studies may delve into crafting innovative biomaterials with comparatively appropriate cost for improved treatment of oral and maxillofacial cancer.

Combining 3D bioprinting with anticancer bacteria represents a promising therapeutic strategy, because it can integrate multiple bacterial strains with functional biomaterials for steady and adjustable release of engineered antitumor bacteria ^[110, 111]. It is anticipated to suppress tumor recurrence and metastasis in oral and maxillofacial malignancies. However, the clinical translation of live bacterial therapies raises critical safety concerns regarding systemic exposure and infection risk, particularly in immuno-compromised cancer patients ^[110, 112]. Confronted with these challenges, biocontainment strategies, such as genetic containment systems and physical encapsulating, are in demand to prevent the accidental proliferation and dissemination of engineered organisms ^[110, 113].

As a result, increasing attention has been directed toward this therapeutic strategy, aiming not only to enhance the treatment efficacy, but also to improve patient prognosis.

6. Conclusion

The integration of 3D bioprinting with functional biomaterials has substantially advanced the management of oral and maxillofacial cancers, offering patient-specific approaches from resection to reconstruction and including supportive treatments such as radiotherapy and drug delivery. These advances have improved treatment precision, enhancement of clinical outcomes, and reduced treatment-related morbidity to some extent. However, regarding extensive clinical translation, 3D bioprinting remains challenging due to issues in hardware and software. It will take

persistent endeavors in solving these obstacles and seeking innovative paths of research for the full exploitation of 3D bioprinting potential and the development of new-generation approaches for the management and treatment of oral and maxillofacial malignancies.

Acknowledgments

None.

Funding

This work was supported by Open Fund of the State Key Laboratory of Fundamental Components and Electromechanical Systems in Fluid Dynamics, Zhejiang University (No. GZKF-202413), and Sichuan Medical Association Scientific Research Project (No. S2024067).

Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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