REVIEW ARTICLE

3D Printing Polymer-based Bolus Used for Radiotherapy

Ying Lu[1,2], Jianbo Song[2], Xiaohong Yao[1], Meiwen An[3]*, Qinying Shi[2], Xiaobo Huang[1]*

[1]Laboratory of Biomaterial Surface and Interface, School of Materials Science and Engineering, Taiyuan University of Technology, Taiyuan 030024, Shanxi Province, China
[2]Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Taiyuan 030032, Shanxi Province, China
[3]Institute of Applied Mechanics and Biomedical Engineering, Taiyuan University of Technology, Taiyuan 030024, Shanxi Province, China

Abstract: Bolus is a kind of auxiliary device used in radiotherapy for the treatment of superficial lesions such as skin cancer. It is commonly used to increase skin dose and overcome the skin-sparing effect. Despite the availability of various commercial boluses, there is currently no bolus that can form full contact with irregular surface of patients' skin, and incomplete contact would result in air gaps. The resulting air gaps can reduce the surface radiation dose, leading to a discrepancy between the delivered dose and planned dose. To avoid this limitation, the customized bolus processed by three-dimensional (3D) printing holds tremendous potential for making radiotherapy more efficient than ever before. This review mainly summarized the recent development of polymers used for processing bolus, 3D printing technologies suitable for polymers, and customization of 3D printing bolus. An ideal material for customizing bolus should not only have the feature of 3D printability for customization, but also possess radiotherapy adjuvant performance as well as other multiple compound properties, including tissue equivalence, biocompatibility, antibacterial activity, and antiphlogosis.

Keywords: Radiotherapy; Bolus; 3D printing; Soft polymers; Hydrogel

1. Introduction

Radiotherapy is an effective way used for the treatment of tumors, especially in areas where surgery is not possible. Almost half of cancer patients receive radiotherapy at certain point of treatment[1]. To provide a sufficient radiation dose to the tumor, the types of radiation that target tumor location should be selected. Conventionally, electron is used to kill tumors of superficial lesions, such as breast cancer, skin cancer, and nasopharyngeal cancer; however, the dose distribution is inhomogeneous and the target coverage is inadequate. It is widely recommended that the target area should receive at least 95% of the predesigned dose when administering radiotherapy[2]. However, because of the skin sparing effect of high-energy photon beams, the superficial lesions cannot

receive a sufficient dose. To solve this problem, a build-up material called bolus, is often placed on the surface of the skin to maximize the radiation dose of subcutaneous tissues so as to achieve the desired dose at target position while reducing the dose in deep tissues[3]. Bolus acts as a layer of skin tissues to provide a more effective treatment to the superficial lesions[4] (**Figure 1**).

Despite the availability of commercial bolus, there are still some problems with bolus during radiotherapy. Most commercial boluses are in a flaky structure that does not form adequate contact with the irregular surface of patients' skin, such as the ear, nose, and scalp, resulting in air gaps between the bolus and the irregular skin[5]. The resulting air gap is very harmful to obtaining the expected distribution of radiation dose at planning target volume (PTV) for achieving a desired therapeutic outcome[6]. The

conventional flat bolus with a uniform size can hardly match the patient's unique body geometry and allow for repeatable setup for treatment[7,8]. Therefore, it is an urgent desire to customize a bolus for fitting any skin contour perfectly in radiotherapy[9-12] (**Figure 2**).

Presently, three-dimensional (3D) printing is one of the ideal means to achieve the customization of various complex structure, especially the personalized medical device[13,14]. At present, some personalized boluses processed by 3D printing have begun to be used in radiotherapy.

Compared to the commercial flat bolus, the 3D-printed bolus allows for a closer match to a patient's skin surface[15,16]. The patient-personalized boluses processed by 3D printing have proven to be close to the
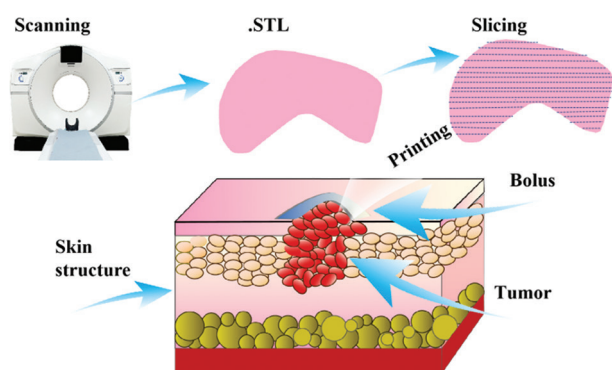

Figure 1. Illustration of bolus for the treatment of superficial tumors by radiotherapy. The tumor (red) is located in the subcutaneous tissues. Bolus (blue) is used to increase skin dose and overcome the skin-sparing effect.

skin and have good efficacy in radiotherapy, but have been limited in practical use due to the shortcomings, including the immaturity of printed materials, inconvenient preparation, and time-consuming preparation.

This review mainly focuses on the very recent advances in the development of 3D printed bolus, which has significant potential in radiotherapy. A systematic searching was performed within PubMed, EMBASE, ScienceDirect, and Scopus investigating terms (3D printing OR 3-dimensional printing OR three-dimensional printing OR rapid prototyping OR additive manufacturing) And (bolus OR polymers) with a careful selection and deep analysis. Only papers published in English between January 2000 and December 2020 were included in the study. This review was organized as follows: the first part shows the main soft polymers used for processing bolus; the second part describes the current 3D printing technologies suitable for processing soft polymer materials; the third part discusses the research status of 3D printing bolus; and the last part presents our perspective and outlook on the development of the 3D printing bolus.

2. Soft polymers used for creating bolus

The use of bolus originally reported as early as 1920 still finds its way in the current radiotherapy[17]. In the history of radiotherapy, various materials, such as water, wet gauze, paraffin, beeswax, and Vaseline, have been used to create bolus[18]. However, there are still many problems in the practical application of most bolus materials, mainly because they have poor fit to skin contour and are uneasy
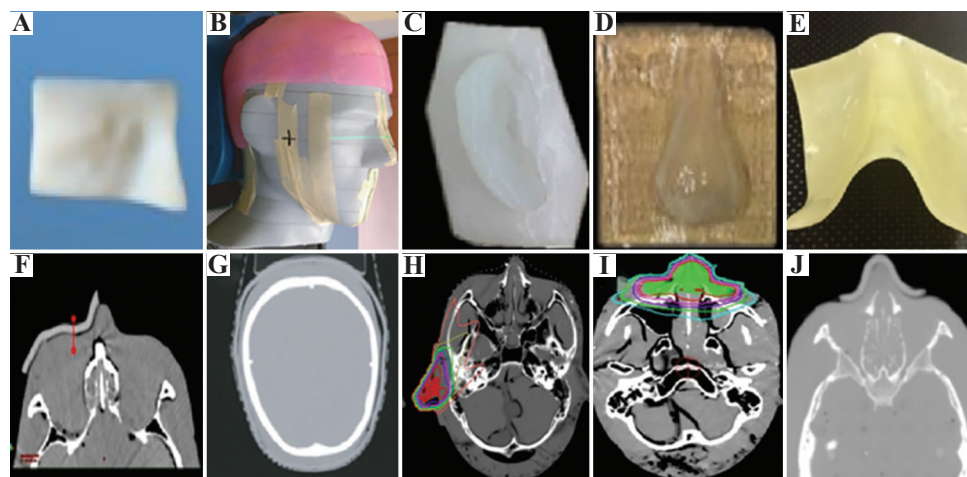

Figure 2. Different boluses and their cross-sectional computed tomography (CT) images. Acrylonitrile butadiene styrene (ABS) bolus (A) and its CT image (B) for head radiotherapy (Reproduced from Ref[8] licensed under Creative Commons Attribution 4.0 license). Agilus-60 bolus (C) and its CT image (D) for head radiotherapy (Reproduced from Ref[9] licensed under Creative Commons Attribution 4.0 license). Silicon bolus (E) and its CT image (F) for ear radiotherapy (Reproduced from Ref[10] licensed under Creative Commons Attribution 4.0 license). Hydrogel bolus (G) and its CT image (H) for nose radiotherapy (Reproduced from Ref[10] licensed under Creative Commons Attribution 4.0 license). PCL bolus (I) and its CT image (J) for nose radiotherapy (Reproduced from Ref[12] licensed under Creative Commons Attribution 4.0 license).

to fabricate. With the development of technology, the modern bolus based on polymers has begun to appear in the field of radiotherapy. Compared to other materials, soft polymers are more suitable for constructing the modern bolus due to their unique physical properties, such as toughness, flexibility, and viscoelasticity. Young's modulus is a key parameter used for defining soft and rigid materials. Human soft tissues, such as skin or muscle tissues, exhibit a modulus of $10^4 - 10^9$ Pa[19] (**Figure 3**); thus, we believe that soft polymers with a modulus in the range of soft tissues have the quality and can be used to construct modern bolus.

Sheet-type boluses are now popular in radiotherapy and are generally used to cover large areas that do not need customization. Superflab is one of the most commonly used commercial boluses due to its excellent tissue equivalency, but they are not moldable[20]. Besides, various soft polymers, such as plastics (resins), hydrogels, silicone elastomers, TangoPlus, and polyurethane (PU), have been used for processing the tissue-equivalent modern bolus. From the viewpoint of materials' physicochemical properties, the application of various polymers in bolus is reviewed in **Table 1**.

2.1. Plastic-based boluses used in radiotherapy

Plastic is a kind of macromolecular polymer, which has been widely used in industry and many fields. Synthetic resin is the most important component in plastics, and thus, the nature of plastic is often determined by the resin due to its large content. According to the physicochemical properties of various plastics, they can be divided into two types: thermosetting plastics and thermoplastics. Thermoplastics melt when heated, cure when cooled, and melt again when heated. Up to now, several thermoplastics including polystyrene, acrylonitrile butadiene styrene (ABS), polycaprolactone (PCL), polylactic acid (PLA), and polyethylene terephthalate–glycol-modified (PETG) have been used for creating bolus.

In radiotherapy, polystyrene is generally considered the gold standard (solid water) in bolus material[21]. It has been reported that a shape memory bolus was designed by tetra-branch PCL with acrylate end groups. The PCL-based bolus shows good adhesion to the body surface and can be processed in a short time[12]. As a form of ABS resin, ABS-M30 (Stratasys, Eden Prairie, MN) resin and ABSplus thermoplastic have also been used to process boluses[22,23]. Park *et al.* reported a PLA-based bolus used for breast cancer radiation therapy[24]. Since the plastic is commonly stiffer than the skin tissues, the poor comfort can cause pain for patients during therapy and air gaps, resulting in the failure of radiotherapy. To improve the fit of bolus to skin contour, the plastic-based boluses were usually customized by the 3D printing technology, especially the fused deposition modeling (FDM) method (the detailed content about 3D printing plastic-based bolus will be discussed in the later parts).

2.2. Elastomer-based boluses used in radiotherapy

The elastomer materials used for creating bolus mainly include silicone and polyurethane (PU). The silicone elastomer refers to a straight chain polymer, whose main chain is composed of silicon atoms and oxygen atoms alternately, and the silicon atoms are usually connected with two organic groups. Compared with the plastic, the silicone elastomers have the flexibility and elasticity
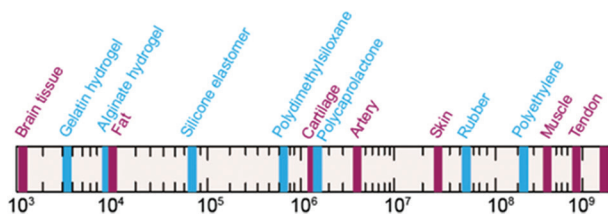

Figure 3. Young's modulus of selected soft polymers (blue) and human tissues (red).

Table 1. Polymer materials used for processing bolus

Categories	Typical materials	Density (g/cm³)	Youngty modulus (Pa)	Advantages	Disadvantages	References
Plastic	PCL Polystyrene ABS PLA PETG	$1.03 - 1.30$	$10^6 - 10^7$	Suitable for processing	Stiff; discomfortable for patients	[12,21-24]
Elastomer	TPU Silicone	$1.05 - 1.25$	$10^4 - 10^9$	Flexible; elastic; biocompatible	Air gaps between bolus and skin	[15,25,26]
Hydrogel	TPU/PAM Methacrylic acid Nanocellulose	$1.05 - 1.32$	$10^2 - 10^4$	Tunable physicochemical property; tissue equivalence; adhesion	Poor mechanical properties	[7,10,27]

closer to the skin tissue. As a representative silicone, polydimethylsiloxane, which is colorless, odorless, transparent and does not cause skin irritation, can be developed into commercial bolus[25]. The polymer has excellent shear resistance, which can ensure its repeated use in radiotherapy. In addition, other silicone elastomers used for processing boluses were also reported. For example, a silicone elastomer based on dihydroxypolysioxane and ethyl polysilicate as the crosslinking agent was synthesized to construct a bolus[10]. Chiu *et al.* have constructed a silicone-based bolus through casting the liquid silicone (EcoFlex 00-30, Smooth-on Inc.)[26]. Due to their chemical stability, excellent biocompatibility, and good mechanical properties, silicone elastomers have great advantages in preparing bolus, but their density $(1.1 - 1.2 \text{ g/cm}^3)$ being slightly different from the skin tissue may lead to a decrease of tissue equivalence. No matter how good the performance of the silicone elastomers, the sheet structure of bolus will always cause air gaps in the treatment of irregular surface of patients' skin.

PU, also known as polycarbamate, is a kind of polymer containing repeated structural units of -O-CO-NH- bonds in its molecular chains. Due to its excellent biocompatibility and flexibility, PU has been widely used to construct medical devices, such as catheters, cardiac aid devices, medical films, artificial skin, and so on[28]. PU-based polymers can be developed by incorporating soft segments (e.g. lactides, caprolactone, and poly(ethylene glycol) [PEG]) or chain extenders in PU backbone. Recently, PU as a bolus material has entered the view of researchers. For example, Zhao *et al.* have used a kind of thermoplastic PU (TPU) to create a bolus for adjuvant treating a recurrent squamous cell carcinoma at the nasal septum[15]. Hou *et al.* have developed a PU-based bolus with multi-functions, including excellent mechanics and adhesive properties, which make it fit closely to the patient's skin with irregular surface[7]. The mechanical properties of PU can be tailor-made according to the structure-property relationship. Therefore, PU is likely to be processed into a bolus with good tissue equivalence. Besides, TangoPlus is another kind of commercial elastomer used to print tissue-equivalent bolus[29].

2.3. Hydrogel-based boluses used in radiotherapy

Hydrogel is a kind of 3D network consisting of hydrophilic polymer chains, which are crosslinked to matrix with high water content. Due to its excellent characteristics, including tunable physicochemical and bioactive properties, versatility in fabrication, high biocompatibility, and similarity to native extracellular matrix, the hydrogel has widely used as promising biomaterials in the biomedical field[30]. Up to now, different hydrogels from both synthetic and natural hydrogels have been developed in various applications, such as tissue

engineering, cell therapy, regenerative medicine, and stem cell and cancer research[31,32]. Synthetic hydrogels, such as poly(vinyl alcohol), polyacrylamide (PAM), and PEG, generally possess precise controllable performance and show high mechanical properties, but lack biological moieties[33-35]. On the other hand, natural hydrogels, such as chitosan, collagen, alginate, gelatin, and hyaluronic acid (HA), have received wide attention due to their bioactive properties. However, their deficiencies include uncontrollable degradation, potential immunogenicity, and low mechanical properties[36-38]. Due to the distinct performance of each of the hydrogel classes, it can be selectively used in various fields according to the application requirements.

Among various materials, hydrogels have the best tissue equivalence due to their similar density and structure to soft tissues. In recent years, hydrogel-based boluses have been studied in the radiotherapy. For example, Kong *et al.* fabricated a bolus composed of methacrylic acid hydrogel, which not only showed good dose parameters in intensity modulated radiation therapy plans, but also had a high degree of comfort and repeatability[10]. Chiozzini *et al.* reported a hydrogel-based bolus consisting of the bacterial nanocellulose, which is made up of D-glucose monomers and produced by several kinds of bacteria[27]. Compared to the commercial bolus, this bolus showed superiority in relation to the radiotherapy parameters, including the radiation attenuation potential and radiological density.

To the best of our knowledge, hydrogel has many advantages including flexibility, odorlessness, nontoxicity, and high transparence, but up to now, it has not been widely used as a bolus in clinical setting. The reason is the quality of losing water easily and the nature of being fragile for the traditional hydrogel. Due to the high-water content (>85%), hydrogels tend to lose water and undergo shrinkage or deformation, which greatly limits their application in radiotherapy. To solve this problem, a water-resisting layer, such as polyol PU membrane or silicone oil, can be used to cover the hydrogel surface to prevent dehydration of hydrogels[10]. An alternate approach is to replace the water in the gel with glycerine, maintaining the structure of hydrogels.

In fact, the main problem limiting the wide application of traditional hydrogels is their poor mechanical behavior, including low stretchability, low toughness, and notch-sensitiveness. For example, the alginate hydrogel is easily ruptured when just stretched to 1.2 times of its original length. Most traditional hydrogels with a fracture energy of about 10 J/m^{-2}, are more brittle than the cartilage with ~1000 J/m^{-2} and natural rubbers with 10,000 J/m^{-2}. When the hydrogels contain notches, the strength and stretchability of samples can be markedly decreased. To solve this problem, various types

of composite hydrogels, including slide-ring hydrogels, double network hydrogels, and nanocomposite hydrogels, have been developed by introducing an effective energy dissipation mechanism[39,40]. For example, a nanocomposite hydrogel composed of hectorite clay and N-isopropylacrylamide has an elongation of up to 1300%. A tough and stretchable hydrogel with double networks was created by mixing covalently crosslinked PAM and ionically crosslinked alginate. The resulting composite hydrogel can be stretched more than 20 times of its original length. It also showed excellent notch-insensitive and self-recovery performance[41]. Hou *et al.* have reported a composite hydrogel (PU/PAM) composed of PU and PAM as bolus. This novel hydrogel with excellent mechanical, self-healing and adhesive properties, can provide an optimal dose distribution for radiotherapy[7]. Over the past decade, major breakthroughs have been made in the research of composite hydrogels with strengthened mechanics. We believe that these advances will lead to a framework that helps construct an ideal bolus in radiotherapy through rational design of hydrogels. Therefore, with the development of hydrogel research, more and more hydrogels will be developed to construct boluses used for radiotherapy in the future.

In this section, we mainly review the current soft polymers used to prepare boluses and analyze the physicochemical properties of these materials as boluses. Compared with plastics, elastomers, and hydrogels with excellent flexibility and tissue equivalence are more suitable to construct boluses. The properties of the material play an important role in radiotherapy, but to form full contact with the irregular surface of patients' skin, the structure of the bolus needs to be customized.

3. 3D printing technology suitable for processing polymers

As a promising additive manufacturing, 3D printing has become a versatile technology for manufacturing 3D structures composed of different materials, such as ceramics, metals, and polymers[42]. According to the digital data of 3D models, the designed 3D objects can be processed layer-by-layer. Different from traditional manufacturing methods, 3D printing can rapidly turn digital-aided designs into 3D complex objects without wasting any materials. According to the printing materials and the principles, print heads or laser optics are generally used to deposit one layer of 3D objects. During the process of printing, the deposited regions are crosslinked or solidified to yield entities[43]. In addition, the ability of 3D printing to quickly produce products on demand has greatly boosted the academic research and the industrial production[44]. Up to now, based on different principles and materials, over dozen types of 3D printing technologies that meet the nature of different materials

have been developed[45]. Especially for polymer materials with various polymerization characteristics, four printing techniques are mainly used, including powder bed fusion, material extrusion, material jetting, and vat polymerization (**Figure 4**). The performance of different printing technologies is listed in **Table 2**.

3.1. Powder bed fusion

As a kind of additive manufacturing process, power bed fusion makes use of a laser to sinter powdered materials. It is also called selective laser sintering (SLS) according to the phase states of powder bonding[46]. With the help of lasers that automatically aim at points in space manipulated by a 3D control system, the powdered materials are bonded together to form a solid structure. The manufacturing process of SLS consists of three repeated steps[47]. First, the powdered materials are uniformly distributed as a printing layer by scraping or rolling. Second, the powder is selectively fused to form a solid structure by scanning the laser. Third, to print the next layer, the build platform descends one layer. These three steps are repeated until the SLS process is finished. Compared to other 3D printing, SLS does not require additional supporting materials. In addition, the powder in the non-molten region can be recycled after printing, resulting in a material utilization rate of close to 100%.

The resolution of SLS printed parts is largely dependent on the particle size: the larger the particle and the lower the spatial resolution. However, for the sake of safety, cost efficiency and process ability, the size of powder particles is usually limited to a range of 10 – 100 μ. Up to now, the resolution of SLS can reach 100 μm under optimal conditions[48].

In general, powdered materials used in SLS should possess several properties, such as compactness, good fluidity, and thermal stability. During the first step of SLS process, good fluidity and compactness are the key factors to ensure proper coalescence in the subsequent sintering. In addition, the most crucial requirement for SLS powders is the thermal properties that allow the powders to solidify uniformly during melting and sintering[49]. As for soft polymer materials used for SLS, these requirements are extraordinarily harsh. At present, few soft polymer powders are processed using SLS, such as polycarbonate (PC), PCL, and thermoplastic elastomers (TPEs). There is a popular view that the biomedical fields are the most active areas for SLS using soft polymer materials[50]; however, SLS is not well suited for processing soft bolus with good softness and tissue equivalence due to its strict requirements for materials.

3.2. Material extrusion

In extrusion printing, the polymer materials are extruded through a nozzle to form a continuous filament, which
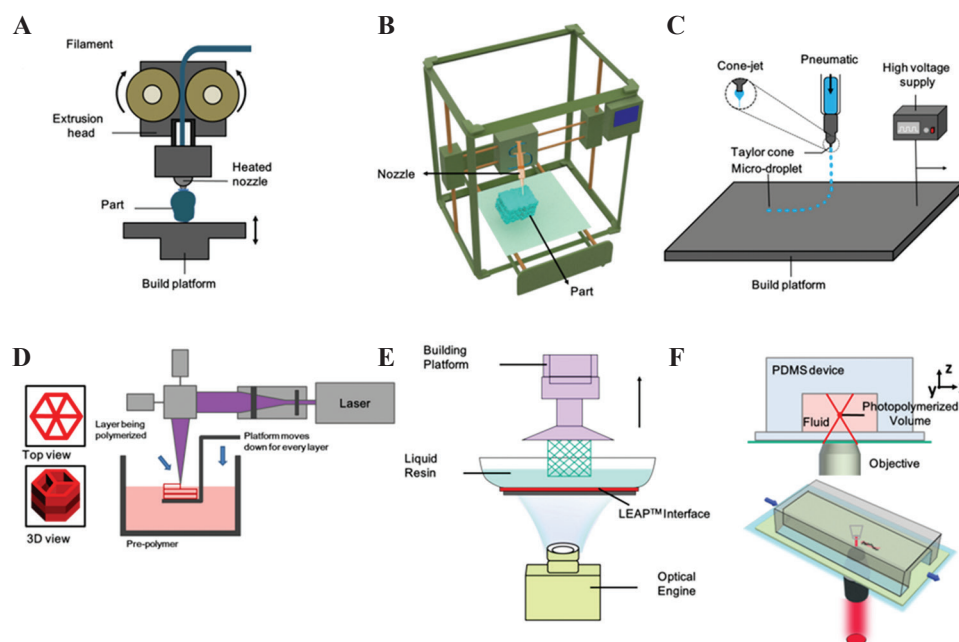
Figure 4. Schematic illustrations of different 3D printing technologies. (A) Fused deposition modeling printing. (B) Direct ink writing printing. (C) Inkjet printing. (D) Stereolithography printing. (E) Digital projection lithography printing. (F) Two-photon polymerization printing.

is deposited to build the target entity. The extruded filament is deposited at the designed position through the movement of the XY axis to complete the pattern of one layer. After finishing one layer, the build platform moves down to deposit the next layer. These steps are repeated until the designed objects are completed[51].

At present, the extrusion printing mainly includes FDM and direct ink writing (DIW). As for the FDM, thermoplastic filaments are liquefied into their semi-molten state using a heated nozzle. The liquefied materials are then solidified when they are cooled below their glass transition temperature. Due to the high viscosity and the swelling of the melted polymer, the resolution of printed structures is greatly reduced to a few 100 μ[52]. In addition to the basic thermoplasticity, the printed materials must maintain a balance between the mechanical performance and the rheological properties, which greatly limits the variety of printable materials. Up to now, several thermoplastic polymers have been used in the FDM, including PCL, ABS, PLA, and other thermoplastics[53]. However, inhomogeneity associated with an FDM printed bolus may also impact the use in radiotherapy.

The DIW method is mainly used to print viscoelastic materials. Compared with the FDM using a heated nozzle, DIW utilizes a common needle to extrude the printed materials[54]. After deposition, the curing processes, including cooling curing and photopolymerization, are used to solidify the printed structures. The viscoelasticity of material is critical for DIW, which requires the rheological property of printed

materials to ensure the printing fidelity and continuity, including yield point and shear thinning[55]. The extrusion of viscoelastic material is considered a transient shear process, which allows the extrusion to be smooth and ensures the deposited filaments retain their shapes. When the inks are extruded from the nozzle, such viscoelastic liquids can recover their initial storage modulus and viscosity. Compared to other printing methods, the DIW process can accept a larger variety of materials that possess such rheological properties. Therefore, a large number of polymer materials can be printed using the DIW, including silicone elastomer, PU, and hydrogels[56]. The main disadvantages of the DIW technology are its slow building speed and low resolution. At present, it has been reported that the resolution of DIW can just reach a few 100 μ and the highest printing speed of DIW is only 100 mm/s, which is greatly less than that of photopolymerization printing[57].

3.3. Material jetting

Inkjet printing is an additive manufacturing technology through which innumerable droplets of printed materials are deposited layer-by-layer to form the target entity[58]. The typical setup of inkjet printing is generally composed of a motion platform with jetting heads, an X-Y-Z three axis, and auxiliary curing devices. Low-viscosity liquids are ejected from the jetting heads to form the droplets, which are deposited on the building platform and then solidified[59]. The inkjet printing needs to meet two basic

Table 2. Comparison of printing methods for bolus

Categories	Methods	Resolution	Building speed	Suitable materials	Potential to print bolus	Advantages	Disadvantages	References
Powder bed fusion	SLS	>100 μl	**	Powdered materials	Poor	High material utilization rate; no support material required	Material limitation; few soft polymer powders	[46-50]
Material extrusion	FDM	>100 μl	**	Thermoplastic polymers	Poor	High simplicity; capability to print compositional gradients	Low speed; low resolution	[51-57]
	DIW	1-100 μ-	**	Pseudoplastic polymer fluids	Poor			
Material jetting	Inkjet printing	>10 μl	***	Polymer fluids with low viscosity	Poor	Applicable for wide range of biomaterials; ability to print multi-material	Clogging of the printing head; expensive setup	[58-62]
Photopolymerization	SLA	>5 μ5	***	Photopolymers with low viscosity including photoresin and photohydrogen	Fair	High resolution; suitable for many photocurable polymers; raw material base is fluid	Material limitation; require an UV source	[63-72]
	TPP	>100 nm	*		Poor			
	DLP	>5 μ5	****		Good			
	CLIP	>100 μl	*****		Good			

requirements, namely, the fluid suitable for ink jetting and the ability to solidify into an entity. As a key process of inkjet printing, the generation of droplets is mainly dependent on both the fluid performance and the 3D printing parameters[60]. The former includes dynamic viscosity (η), fluid density (ρ) and surface tension (γ), and the latter encompasses the velocity of the ejected fluid (v), the droplet length (l), and the nozzle diameter (d). The inkjet printing can be achieved only when these parameters are controlled in an appropriate processing condition[61].

The dimensionless Z parameter is generally used to determine whether the liquids can be ejected stably. As for the high values of Z, the ejected droplets are easily to splash into multiple satellite droplets, whereas at low values of Z, the droplet ejection will be prevented by viscous dissipation. In general, stable jetting can be generated when Z is controlled between 1 and 10[62].

Due to such stringent requirements, few polymers can be printed by inkjet printing. Among these polymers, because many hydrogels have excellent inkjet printing performance, inkjet printing hydrogels have become a very hot topic[60]. Nowadays, the advanced inkjet printing technology possesses a powerful ability to rapidly construct complex 3D structures using multi-nozzle arrays, which can eject more than 100 million droplets per second[42]. In fact, it is difficult to eject complex fluids without clogging, limiting the diversity of printable polymers.

3.4. Vat polymerization

As a kind of additive manufacturing process with great potential, photocuring printing uses ultraviolet (UV) light to selectively solidify liquid photosensitive polymers by photocuring layer-by-layer to obtain the target object[63,64]. Up to now, the photopolymerization printing technology mainly includes stereolithography (SLA), digital projection lithography (DLP), two-photon polymerization (TPP), and computed axial lithography (CAL).

SLA is the first photocuring printing developed in the early 1980s. The SLA uses a point light source (e.g. laser) to irradiate only one voxel at a time and prints patterns with the movement of the beam. After one layer is completed, the building plate moves by one-layer thickness and a new layer of liquid photosensitive polymers turns into the printing regions to print the next layer. These procedures are repeated layer-by-layer until the printing of the desired object entity is accomplished[65,66]. In general, the photocuring resin is mainly used as the printed material of SLA to fabricate 3D objects with large size in the manufacturing industry.

In TPP, two laser pulses with high wavelengths intersect to generate a single pulse with a low wavelength, which stimulates the polymerization[67]. Compared to the SLA possessing a focal plane, the TPP gets a focal spot. Thus, the accuracy of TPP is generally higher than SLA. It is reported that the optimal printing resolution of the TPP so far is around 100 nm[68]. TPP is normally used to fabricate 3D sophisticated objects within several micrometers, but the printing dimensions are very small, usually limited in 1 cm³. For example, using this method, PEGDA gels were processed into 3D helix-shaped constructs in micron grade[69]. In summary, these two laser-based prototyping techniques possess the characteristic of high precision and resolution. However, the processing speed of SLA and TPP is relatively slow, which may make 3D printing bolus challenging.

To increase the manufacturing speed of photopolymerization, researchers have developed the DLP technology[70], which makes an entire pattern on the focal plane to be crosslinked simultaneously. In this method, a dynamic pattern can be projected by using a liquid crystal display or a digital micro-mirror device[43,71]. Therefore, the printing speed of DLP is significantly improved in comparison to the point light technology. Recently, continuous liquid interface production (CLIP) technology, which is an advanced DLP technology with higher printing speed has been developed. The CLIP can achieve the continuity of printing by forming a polymerization "dead zone," which allows the 3D objects to be printed in minutes instead of hours[42].

Recently, a novel photocuring printing technology named CAL was developed. By irradiating a rotating volume of photosensitive polymers with a dynamically changing light pattern, CAL can obtain the concurrent printing of all points within a 3D object[71]. The conventional photocuring printing, such as DLP, prints objects layer-by-layer, whereas the CAL delivers light energy to the material volume in the form of a series of 2D images. Each image projection is propagated through the material volume at a different angle. The superposition of light energy causes the whole entity to solidify at 1 time in accordance with the designed geometry. It has been reported that the printing time for a centimeter-scale object just needed about 30 – 120 s, which is greatly faster than the layer-by-layer printing method. However, the resolution of CAL is limited to sub-millimeters[72].

In summary, polymers suitable for most photopolymerization printing should obtain two basic characteristics: good fluidity and photocurable ability[73]. The photopolymers should be liquid with low viscosity so that the polymers can be evenly spread within the printable area. In general, the photopolymers have a specific group, which can be induced to undergo photo crosslinking reactions triggered by the initiators. In addition to the initiators and the photopolymers, other additives are also used to improve the printing quality,

including light absorbers, radical inhibitors, and diluents. The light absorbers can restrain the curing depth, the radical inhibitors can prevent premature solidification of liquids, and the diluents can decrease the liquid viscosity[74]. Compared to the large polymer family, the variety of photopolymers is relatively small. Novel photopolymers can be developed by grafting specific photosensitive groups with normal polymers. Up to now, various photopolymers have been used for photocuring printing, including photocuring resins, hydrogels, and silicone elastomers[75].

4. Customization of bolus through 3D printing

With the improvement of 3D printing technology, it has been widely used in various fields, especially the biomedical field requiring customization of medical devices. 3D printing is currently a promising approach to achieve the customization of bolus. Compared to the commonly used flat bolus, the 3D-printed bolus allows for a more match to a patient's skin surface and shows desirable curative effect of radiotherapy (**Figure 5**). However, 3D printing bolus still stays in the early stages of development due to shortcomings of printable and appropriate materials. Reviewing the research progress of 3D printing bolus in recent years, we divide the current 3D printing bolus into two main categories: indirect printing and direct printing. The former is to first print a shell of the bolus and then fill it with other polymers, and the latter is to print a bolus directly with a 3D printing technique.

4.1. Indirect printing bolus (casting)

As the name suggests, the indirect printing means that it takes at least two steps to produce a customized bolus. The typical workflow to make bolus by the indirect printing is shown in **Figure 6A**. In this method, the bolus shells are first printed by 3D printing technology, then the materials were cast into the chamber of shells. After demolding, a customized bolus is obtained. To be precise, this method should be called casting, which is suitable for processing most of hydrogels and some elastomers with low melting point. Up to now, various polymers have been widely processed as customized bolus using this method. For example, Kong *et al.* printed a shell of bolus using the PLA and then filled it with silicone rubber and hydrogels for non-melanoma skin cancer radiotherapy[10]. Park *et al.* casted a urethane liquid rubber and liquid silicon compound into the mold to make the customized boluses[81]. Resins are commonly used to print mold shells due to their high stiffness, low swellability, and low flexibility. Compared to the commonly used sheet bolus, the bolus cast by this method can contact closer with the body, greatly
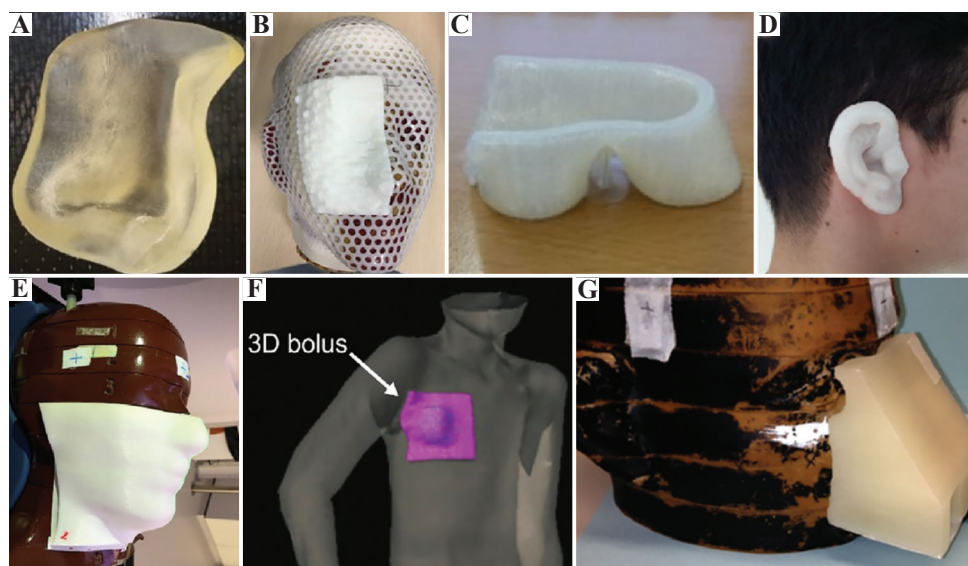

Figure 5. Some 3D-printed boluses reported in the literature. (A) A nose bolus printed with Tangoplus (Reproduced from Ref[76] licensed under Creative Commons Attribution 4.0 license). (B) A bolus printed with ABS on the head phantom surface (Reproduced from Ref[77] licensed under Creative Commons Attribution 4.0 license). (C) 3D-printed bolus of the 4th and 5th knuckle (Reproduced from Ref[8] licensed under Creative Commons Attribution 4.0 license). (D) 3D-printed bolus fitting the ear of a volunteer (Reproduced from Ref[8] licensed under Creative Commons Attribution 4.0 license). (E) 3D-printed Ninjaflex bolus covering the right-hand side of the head phantom (Reproduced from Ref[78] licensed under Creative Commons Attribution 4.0 license). (F) 3D-printed breast bolus (Reproduced from Ref[79] licensed under Creative Commons Attribution 4.0 license). (G) Bolus printed with PLA on the Alderson RANDO phantom (Reproduced from Ref[80] licensed under Creative Commons Attribution 4.0 license).

reducing the air gap and improving the efficiency of radiotherapy.

However, the indirect printing method is complicated and time-consuming, and the accuracy of this method is relatively low. The process of this method mainly includes molding and casting, which determines the preparing efficiency of customized bolus. Chiu *et al.* have constructed a silicone bolus using this method for head-and-neck radiotherapy. The time taken for construction including mold printing and fillers casting is about 2 days depending on bolus surface area, complexity and volume[26]. In this method, two pieces of mold shells including a positive and a negative are first printed and then put together to form a chamber for casting fillers. The accuracy of the bolus is seriously influenced by the thickness of mold shells. This method is suitable for the preparation of bolus with a large size used for breast or head radiotherapy, but not for small bolus with complex structures used for ear or nose. In a word, although the indirect printing method enables the customization of bolus and improves the efficiency of radiotherapy to some extent, the complicated and time-consuming process will greatly limit the commercialization of this technology in the field of radiotherapy.

4.2. Direct printing bolus

Direct printing means that 3D objects can be directly realized from CAD models by means of computer numerical control printers. CAD models are translated into computer-readable formats (usually standard tessellation language file), and then sliced into control codes which can control printers to solidify material in a layer-by-layer manner[76] (**Figure 6B**). With the rapid development of 3D printing technology, increasing researchers from different backgrounds have started to manufacture devices or structures with high complexity using this powerful technology[8,77,78]. In recent years, the customized bolus directly processed using 3D printing has also attracted wide attention of doctors and scholars in the field of radiotherapy.

Up to now, various polymers have been used to fabricate bolus using different 3D printing technologies, mainly including FDM, inkjet and SLA[79,80]. FDM is one of the earliest 3D printing technologies used to print bolus. For example, Kim *et al.* have used the FDM method to print a nose bolus using ABS resins as the printing material[22]. Using ABSplus thermoplastic as printing materials, Park *et al.* have fabricated a customized ear bolus by applying the FDM method[82]. A customized breast bolus composed of PLA was also printed by means of this method[24]. Through this method, a semi-flexible TPU was processed into a customized leg bolus used for treating the primary cutaneous lymphoma[83]. In the current study, the thermoplastic polymers were mainly used to process customized bolus based on the printing principle of FDM technology. Compared with both the commercial sheet bolus and the indirectly printed bolus, the customized bolus processed by FDM has a better fit to the irregular body skin. However, these thermoplastic polymers used for FDM are stiffer than the soft tissues. It inevitably results in the patient experiencing pain and air gaps, influencing the efficiency of radiotherapy. In addition, the time required for preparing a customized bolus using this method was relatively long due to the time-consuming process of FDM. Consequently, a more malleable and printable polymer should be used to process customized bolus.

Recently, some other 3D printing technologies suitable for processing soft polymers have begun to be used to produce customized bolus. Park *et al.* used an inkjet printing technology to print a nose bolus composed of a malleable rubber-like material[76]. Using the same method, Baltz *et al.* also made a customized bolus cap composed of a rubber-like photopolymer resin used for
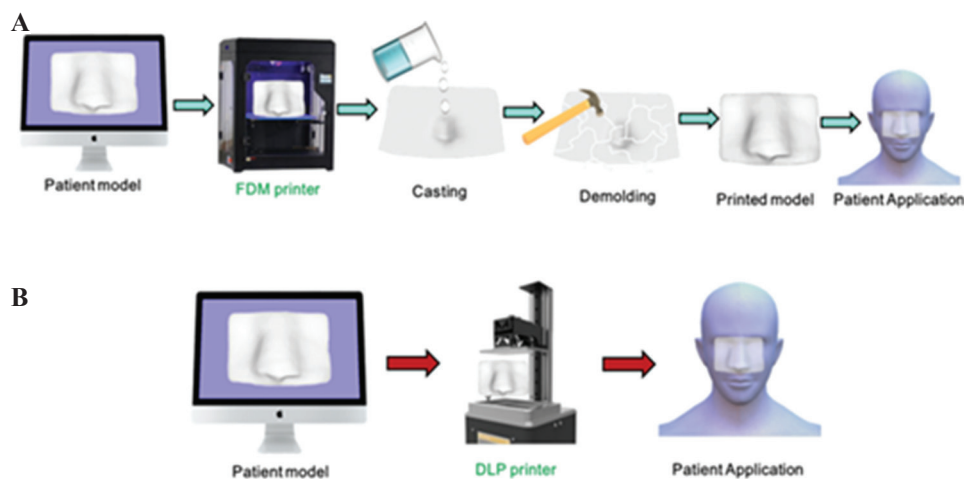

Figure 6. (A) Indirect printing workflow of bolus. (B) Direct printing workflow of bolus.

total scalp irradiation[9]. In addition, Munoz *et al.* used SLA method to create a customized nose bolus composed of elastomeric materials, which showed compliant, elastic, and water equivalent properties[84]. Compared to the rigid bolus, the soft bolus created by these two methods greatly reduces the patient discomfort and unwanted air gaps. It suggests that the customization of bolus is not only related with the selection of 3D printing methods, but also dependent on the properties of printed materials.

Direct printing is a promising approach to rapidly achieve the customization of bolus, but 3D printing of bolus using soft polymers is still in the early stage of development. An ideal bolus should not only provide a close contact with the patients' irregular surface, but also possess excellent properties, such as flexibility, biocompatibility, and adhesion. The 3D printing methods determine the printing speed and printing accuracy of bolus, while the printed materials mainly influence the performance of bolus. With the current 3D printing technology, the bottleneck restricting the application of 3D printed bolus is mainly the deficient development of printable polymer materials. The advances in materials science and 3D printing technology lead to the development of more printable polymers, which will be used for 3D printing of bolus.

5. Summary and outlook

Various materials that are able to be processed into bolus have been used in radiation therapy, but the development of customized bolus prepared by 3D printing of polymers is still in its infancy. To achieve the personalized customization of bolus, this review aims at providing comprehensive insights into the 3D printing bolus. How to choose an appropriate 3D printing technique and to design a suitable printable polymer is an urgent issue to be solved in customizing bolus. We focus on three points: (i) polymer materials used for fabricating bolus, (ii) 3D printing techniques suitable for processing polymer materials, and (iii) personalized customization of bolus through 3D printing technology.

Various 3D printing techniques utilizing different principle to pattern are suitable for different materials. The choice of 3D printing methods is mainly determined by the actual requirements of application[85]. A 3D printing technique suitable for processing bolus should have the following three characteristics: rapid printing speed (<1 h), medium printing scale (X-Y-Z three axis ≤30 cm), and general printing accuracy (≤200 μm). The extrusion printing and the inkjet printing utilize a nozzle to deliver the polymers to the designed position and solidify the polymers by a curing process. As for the nozzle-based printing techniques, most polymers can be printed as long as they have suitable rheological properties. However, the point-to-point printing mode

results in a slow printing speed, which will greatly limit the manufacturing efficiency of personalized bolus. In contrast, photocuring printing can selectively solidify the polymers from a liquid tank, which can perform the patterning process and curing process at the same time. Especially for the DLP- and CLIP-based layer-by-layer printing mode, these photocuring printing methods enable the direct and rapid construction of bolus. As an emerging photocuring printing technology, the CAL shows a faster patterning speed in comparison to the DLP method. However, this technology is premature, costly, and the printing precision is still relatively low. Therefore, among different 3D printing techniques, the DLP and CLIP methods based on layer photocuring are probably the most ideal technology to print personalized bolus at present.

Up to now, the printable materials suitable for DLP-based photocuring printing are mainly photosensitive resins, which have the basic characteristic of photocurability[86]. Photosensitive resins are a class of relatively mature photocurable prepolymers with low molecular weights, which mainly include esterified acrylate epoxy resin, unsaturated polyester, PU, and polymercaptan/polyene photocurable resin systems[87]. Although the photo-resins (Young modulus, ~GPa) have been widely used in the manufacturing industry, they are not suitable for constructing bolus by DLP-based printing due to their higher hardness compared to patients' skin tissues (~KPa). The mismatching in hardness between bolus and skin tissues will inevitably lead to the failure of radiotherapy. Besides, the potential toxicity of photo-resin makes it even less likely to be used in clinic. Therefore, it is urgent to develop a kind of material that can not only be used for DLP printing, but also has an elastic modulus equivalent to skin tissues.

Hydrogels and silicon gels have an elastic modulus close to that of human skin tissue, while most of these materials cannot be directly used for photocuring printing due to a lack of photosensitive properties. To endow the gels with photocurable ability, some photopolymerizable functional groups have been grafted onto the molecular chain of the gels. The modified gels with both photocurable ability and bionic hardness will be a kind of ideal materials for constructing bolus. In addition, it has been recognized that the bolus-assisted radiotherapy can efficiently control the recurrence of subcutaneous tumor, but it also causes some side effects. For example, it is likely to damage the normal tissues around tumors and cause dermatitis in the exposed areas. More severely, inflamed areas are susceptible to bacterial infection, which may prevent irradiated skin from healing and even aggravate skin necrosis. Therefore, to improve the curative effect of radiotherapy, it is urgent and necessary to design a new-type bolus with combined features, including printability,
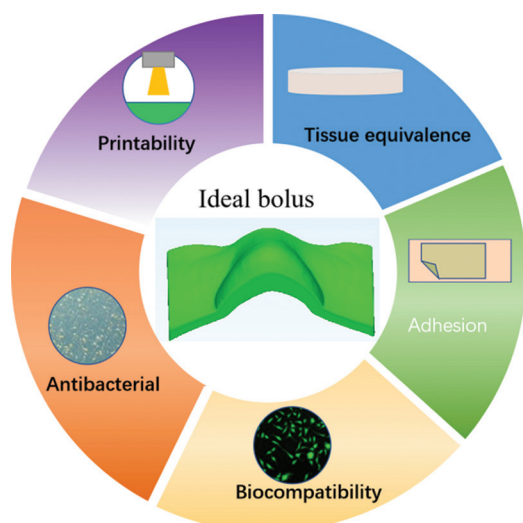
Figure 7. An ideal soft polymer suitable for customized bolus should have combined features, including printability, tissue equivalence, biocompatibility, flexibility, and antibacterial properties.

biocompatibility, good-fit to skin contour as well as antibacterial and antiphlogosis properties (**Figure 7**).

In brief, there has been impressive progress in the application of 3D printing technology in many areas. However, as an emerging technology used in radiotherapy, 3D printing still faces numerous challenges before practical applications, including printing methods, printable materials, and boluses' design. Through reviewing the 3D printing techniques and polymers suitable for processing bolus, we anticipate this review could help readers choose suitable printing methods and design printable polymer materials to achieve the customization of bolus.

An ideal 3D-printed bolus for radiotherapy is an auxiliary device that should integrate multiple properties, including customizable dimensions, appropriate physicochemical performance, and favorable compatibility and antibacterial activity. (i) The customizable dimension is the primary feature of the 3D printed bolus. The conventional bolus is usually a kind of square film with uniform thickness (5 mm), while the 3D printed bolus is an irregular membrane tailored to the characteristics of the patient's skin surface. Compared to the conventional bolus, the 3D printed bolus allows for a more match to the human body, such as the head, breast, and facial parts, and ensures the expected dose distribution at PTV. (ii) The appropriate physicochemical properties of 3D printed bolus mainly include the tissue equivalence, transparency, mechanical performance, and bioadhesion. The bolus is considered a kind of tissue equivalence, which can simulate the absorption and scattering properties of skin tissues for a given irradiation. Although transparency does not normally affect the effects of radiation,

good transparency (≥50%) will help to facilitate the accurate and repeatable placement of bolus. Good mechanical performance means that the bolus not only has an elastic modulus similar to the skin tissues, but also good toughness to prevent it from being torn in repeated use. The bioadhesive performance enables the 3D printed bolus to fit well with the irregular human skin, ensuring the accuracy of radiation dose. (iii) The favorable compatibility means that an ideal 3D-printed bolus should not generate any adverse effects in contact with human body. Besides, antibacterial properties can inhibit the occurrence of inflammation caused by the side effect of radiotherapy. Therefore, to obtain an ideal 3D printed bolus, the convergence of versatility in the soft polymers is inevitable in the future, and is thought to accelerate the outcome of radiotherapy.

Acknowledgments

Conflicts of Interest

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

Author contributions

Y.L. collected information and drafted the manuscript. J.S. advised the organization of the main contents. X.Y. and M.A. reviewed the manuscript. Q.S. collected the detailed research results. X.H. conceived the ideas and edited the manuscript.

References

1. Baskar R, Lee KA, Yeo R, *et al.*, 2012, Cancer and Radiation Therapy: Current Advances and Future Directions. *Int J Med Sci*, 9:193–9.

2. Hodapp N, 2012, The ICRU Report 83: Prescribing, Recording and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). *Strahlenther Onkol*, 188:97–9.
   https://doi.org/10.1093/jicru_ndq002

3. Babic S, Kerr A T, Westerland M, *et al.*, 2002, Examination of Jeltrate Plus as a Tissue Equivalent Bolus Material. *J Appl Clin Med Phys*, 3:170–5.
   https://doi.org/10.1120/1.1471552

4. Hsu SH, Roberson PL, Chen Y, *et al.*, 2008, Assessment of Skin Dose for Breast Chest Wall Radiotherapy as a Function

of Bolus Material. *Phys Med Biol*, 53:2593–606.
https://doi.org/10.1088/0031-9155/53/10/010

5. Aras S, Tanzer İO, 2020, Dosimetric comparison of superflab and specially prepared bolus materials used in radiotherapy practice. *Eur J Breast Health*, 16:167–70.
https://doi.org/10.5152/ejbh.2020.5041

6. Khan Y, Villarreal-Barajas JE, Udowicz M, *et al.*, 2013, Clinical and Dosimetric Implications of Air Gaps between Bolus and Skin Surface during Radiation Therapy. *J Cancer Ther*, 4:1251–5.
https://doi.org/10.4236/jct.2013.47147

7. Hou Y, Song Y, Sun X, *et al.*, 2020, Multifunctional Composite Hydrogel Bolus with Combined Self-Healing, Antibacterial and Adhesive Functions for Radiotherapy. *J Mater Chem B*, 8:2627–35.
https://doi.org/10.1039/c9tb02967b

8. Dipasquale G, Poirier A, Sprunger Y, *et al.*, 2018, Improving 3D-Printing of Megavoltage X-Rays Radiotherapy Bolus with Surface-Scanner. *Radiat Oncol*, 13:203.
https://doi.org/10.1186/s13014-018-1148-1

9. Baltz GC, Chi PM, Wong PF, *et al.*, 2019, Development and Validation of a 3D-Printed Bolus Cap for Total Scalp Irradiation. *J Appl Clin Med Phys*, 20:89–96.
https://doi.org/10.1002/acm2.12552

10. Kong Y, Yan T, Sun Y, *et al.*, 2019, A Dosimetric Study on the Use of 3D-Printed Customized Boluses in Photon Therapy: A Hydrogel and Silica Gel Study. *J Appl Clin Med Phys*, 20:348–55.
https://doi.org/10.1002/acm2.12489

11. Robar JL, Moran K, Allan J, *et al.*, 2018, Intrapatient Study Comparing 3D Printed Bolus Versus Standard Vinyl Gel Sheet Bolus for Postmastectomy Chest Wall Radiation Therapy. *Pract Radiat Oncol*, 8:221–9.
https://doi.org/10.1016/j.prro.2017.12.008

12. Aoyama T, Uto K, Shimizu H, *et al.*, 2020, Physical and Dosimetric Characterization of Thermoset Shape Memory Bolus Developed for Radiotherapy. *Med Phys*, 47:6103–12.
https://doi.org/10.1002/mp.14516

13. Asfia A, Novak JI, Mohammed MI, *et al.*, 2020, A Review of 3D Printed Patient Specific Immobilisation Devices in Radiotherapy. *Phys Imaging Radiat Oncol*, 13:30–5.
https://doi.org/10.1016/j.phro.2020.03.003

14. Zemnick C, Woodhouse SA, Gewanter RM, *et al.*, 2007, Rapid Prototyping Technique for Creating a Radiation Shield. *J Prosthet Dent*, 97:236–41.
https://doi.org/10.1016/j.prosdent.2007.02.005

15. Zhao Y, Moran K, Yewondwossen M, *et al.*, 2017, Clinical Applications of 3-Dimensional Printing in Radiation Therapy. *Med Dosim*, 42:150–5.

16. Tino R, Leary M, Yeo A, *et al.*, 2020, Additive Manufacturing in Radiation Oncology: A Review of Clinical Practice, Emerging Trends and Research Opportunities. *Int J Extrem Manuf*, 2:012003.
https://doi.org/10.1088/2631-7990/ab70af

17. Walker M, Cohen N, Menchaca D, 2005, Play-Doh and Water-Soaked Gauze Sponges as Alternative Bolus Material For Cobalt-60 Teletherapy. *Vet Radiol Ultrasound*, 46:179–81.
https://doi.org/10.1111/j.1740-8261.2005.00033.x

18. Vyas V, Palmer L, Mudge R, *et al.*, 2013, On Bolus for Megavoltage Photon and Electron Radiation Therapy. *Med Dosim*, 38:268–73.
https://doi.org/10.1016/j.meddos.2013.02.007

19. Rus D, Tolley MT, 2015, Design, Fabrication and Control of soft Robots. *Nature*, 521:467–75.
https://doi.org/10.1038/nature14543

20. Benoit J, Pruitt AF, Thrall DE, 2009, Effect of Wetness Level on the Suitability of Wet Gauze as a Substitute for Superflab as a Bolus Material for use with 6mv Photons. *Vet Radiol Ultrasound*, 50:555–9.
https://doi.org/10.1111/j.1740-8261.2009.01573.x

21. Reft CS, 1989, Output Calibration in Solid Water for High Energy Photon Beams. *Med Phys*, 16:299–301.
https://doi.org/10.1118/1.596423

22. Kim SW, Shin HJ, Kay CS, *et al.*, 2014, A customized Bolus Produced Using a 3-Dimensional Printer for Radiotherapy. *PLoS One*, 9:e110746.
https://doi.org/10.1371/journal.pone.0110746

23. Lukowiak M, Jezierska K, Boehlke M, *et al.*, 2017, Utilization of a 3D Printer to Fabricate Boluses used for Electron Therapy of Skin Lesions of the Eye Canthi. *J Appl Clin Med Phys*, 18:76–81.

24. Park SY, Choi CH, Park JM, *et al.*, 2016, A Patient-Specific Polylactic Acid Bolus Made by a 3D Printer for Breast Cancer Radiation Therapy. *PLoS One*, 11:e0168063.
https://doi.org/10.1371/journal.pone.0168063

25. Banerjee SL, Samanta S, Sarkar S, *et al.*, 2020, A Self-Healable and Antifouling Hydrogel Based on PDMS Centered ABA Tri-Block Copolymer Polymersomes: A Potential Material for Therapeutic Contact Lenses. *J Mater Chem B*, 8:226–43.
https://doi.org/10.1039/c9tb00949c

26. Chiu T, Tan J, Brenner M, *et al.*, 2018, Three-Dimensional Printer-Aided Casting of Soft, Custom Silicone Boluses (SCSBs) for Head and Neck Radiation Therapy. *Pract Radiat*

Oncol, 8:e167–4.

https://doi.org/10.1016/j.prro.2017.11.001

27. Chiozzini GC, Mendes GP, Vanni FP, *et al.*, 2020, Bacterial nanocellulose membrane as bolus in radiotherapy: "Proof of concept". *Cellulose*, 28:607–13.

https://doi.org/10.1007/s10570-020-03579-8

28. Cooke SL, Whittington AR, 2016, Influence of Therapeutic Radiation on Polycaprolactone and Polyurethane Biomaterials. *Mater Sci Eng C Mater Biol Appl*, 60:78–83.

29. Bil M, Kijeńska-Gawrońska E, Głodkowska-Mrówka E, *et al.*, 2020, Design and *In Vitro* Evaluation of Electrospun Shape Memory Polyurethanes for Self-Fitting Tissue Engineering Grafts and Drug Delivery Systems. *Mater Sci Eng C Mater Biol Appl*, 110:110675.

https://doi.org/10.1016/j.msec.2020.110675

30. Eslahi N, Abdorahim M, Simchi A, 2016, Smart Polymeric Hydrogels for Cartilage Tissue Engineering: A Review on the Chemistry and Biological Functions. *Biomacromolecules*, 17:3441–63.

https://doi.org/10.1021/acs.biomac.6b01235

31. Ng WL, Chua CK, Shen YF, 2019, Print Me An Organ! Why We Are Not There Yet. *Prog Polym Sci*, 97:101145.

https://doi.org/10.1016/j.progpolymsci.2019.101145

32. Askari M, Naniz MA, Kouhi M, *et al.*, 2021, Recent Progress in Extrusion 3D Bioprinting of Hydrogel Biomaterials for Tissue Regeneration: A Comprehensive Review with Focus on Advanced Fabrication Techniques. *Biomater Sci*, 9:535–73.

https://doi.org/10.1039/d0bm00973c

33. Tao G, Wang Y, Cai R, *et al.*, 2019, Design and Performance of Sericin/Poly(Vinyl Alcohol) Hydrogel as a Drug Delivery Carrier for Potential Wound Dressing Application. *Mater Sci Eng C Mater Biol Appl*, 101:341–51.

https://doi.org/10.1016/j.msec.2019.03.111

34. Wang T, Qu G, Wang C, *et al.*, 2019, Importance of Polyacrylamide Hydrogel Diverse Chains and Cross-Linking Density for Cell Proliferation, Aging, and Death. *Langmuir*, 35:13999–4006.

https://doi.org/10.1021/acs.langmuir.9b02799.s001

35. An H, Zhu L, Shen J, *et al.*, 2020, Self-Healing PEG-Poly (Aspartic Acid) Hydrogel with Rapid Shape Recovery and Drug Release. *Colloids Surf B Biointerfaces*, 185:110601.

https://doi.org/10.1016/j.colsurfb.2019.110601

36. Hussain Z, Thu HE, Shuid AN, *et al.*, 2018, Recent Advances in Polymer-based Wound Dressings for the Treatment of Diabetic Foot Ulcer: An Overview of State-of-the-Art. *Curr Drug Targets*, 19:527–50.

https://doi.org/10.2174/1389450118666170704132523

37. Bonani W, Cagol N, Maniglio D, 2020, Alginate Hydrogels: A Tool for 3D Cell Encapsulation, Tissue Engineering, and Biofabrication. *Adv Exp Med Biol*, 1250:49–61.

https://doi.org/10.1007/978-981-15-3262-7_4

38. Xu J, Zheng S, Hu X, 2020, Advances in the Research of Bioinks Based on Natural Collagen, Polysaccharide and Their Derivatives for Skin 3D Bioprinting. *Polymers* (*Basel*), 12:1237.

https://doi.org/10.3390/polym12061237

39. Haq MA, Su Y, Wang D, 2017, Mechanical Properties of PNIPAM Based Hydrogels: A Review. *Mater Sci Eng C Mater Biol Appl*, 70:842–55.

40. Zhang B, Li S, Hingorani H, *et al.*, 2018, Highly Stretchable Hydrogels for UV Curing Based High-Resolution Multimaterial 3D Printing. *J Mater Chem B*, 6:3246–53.

https://doi.org/10.1039/c8tb00673c

41. Sun JY, Zhao X, Illeperuma WR, *et al.*, 2012, Highly Stretchable and Tough Hydrogels. *Nature*, 489:133–6.

42. Truby RL, Lewis JA, 2016, Printing Soft Matter in Three Dimensions. *Nature*, 540:371–8.

https://doi.org/10.1038/nature21003

43. Zhu W, Ma X, Gou M, *et al.*, 2016, 3D Printing of Functional Biomaterials for Tissue Engineering. *Curr Opin Biotechnol*, 40:103–12.

44. Murphy SV, Atala A, 2014, 3D Bioprinting of Tissues and Organs. *Nat Biotechnol*, 32:773–85.

https://doi.org/10.1038/nbt.2958

45. Zhou LY, Fu J, He Y, 2020, A Review of 3D Printing Technologies for Soft Polymer Materials. *Adv Funct Mater*, 30:2000187.

https://doi.org/10.1002/adfm.202000187

46. Kinstlinger IS, Bastian A, Paulsen SJ, *et al.*, 2016, Open-Source Selective Laser Sintering (OpenSLS) of Nylon and Biocompatible Polycaprolactone. *PLoS One*, 11:e0147399.

https://doi.org/10.1371/journal.pone.0147399

47. Soe SP, Eyers DR, Setchi R, 2013, Assessment of Non-Uniform Shrinkage in the Laser Sintering of Polymer Materials. *Int J Adv Manuf Technol*, 68:111–25.

https://doi.org/10.1007/s00170-012-4712-0

48. Liu K, Sun H, Tan Y, *et al.*, 2016, Additive Manufacturing of Traditional Ceramic Powder Via Selective Laser Sintering with Cold Isostatic Pressing. *Int J Adv Manuf Technol*, 90:945–52.

https://doi.org/10.1007/s00170-016-9441-3

49. Novitsky TF, Mathias LJ, Osborn S, *et al.*, 2012, Synthesis and Thermal Behavior of Polyamide 12, T Random and

Block Copolymers. *Macromol Symp*, 313–314:90–9.
https://doi.org/10.1002/masy.201250310

50. Gu D, Wang H, Zhang G, 2014, Selective Laser Melting Additive Manufacturing of Ti-Based Nanocomposites: The Role of Nanopowder. *Metall Mater Trans A*, 45:464–76.
https://doi.org/10.1007/s11661-013-1968-4

51. Ramanath HS, Chua CK, Leong KF, *et al.*, 2008, Melt Flow Behaviour of Poly-Epsilon-Caprolactone in Fused Deposition Modelling. *J Mater Sci Mater Med*, 19:2541–50.
https://doi.org/10.1007/s10856-007-3203-6

52. Heras ES, Haro FB, 2018, Filament Advance Detection Sensor for Fused Deposition Modelling 3D Printers. *Sensors (Basel)*, 18:1495.
https://doi.org/10.3390/s18051495

53. Hrynevich A, Elçi B, Haigh JN, *et al.*, 2018, Dimension-Based Design of Melt Electrowritten Scaffolds. *Small*, 14:e1800232.
https://doi.org/10.1002/smll.201800232

54. Cheng Y, Chan KH, Wang XQ, *et al.*, 2019, Direct-Ink-Write 3D Printing of Hydrogels into Biomimetic Soft Robots. *ACS Nano*, 13:13176–84.
https://doi.org/10.1021/acsnano.9b06144

55. Paxton N, Smolan W, Böck T, *et al.*, 2017, Proposal to Assess Printability of Bioinks for Extrusion-Based Bioprinting and Evaluation of Rheological Properties Governing Bioprintability. *Biofabrication*, 9:044107.
https://doi.org/10.1088/1758-5090/aa8dd8

56. Zhou LY, 2019, Multimaterial 3D Printing of Highly Stretchable Silicone Elastomers. *ACS Appl Mater Interfaces*, 11:23573–83.
https://doi.org/10.1021/acsami.9b04873

57. Kim Y, Yuk H, Zhao R, *et al.*, 2018, Printing Ferromagnetic Domains for Untethered Fast-Transforming Soft Materials. *Nature*, 558:274–9.
https://doi.org/10.1038/s41586-018-0185-0

58. Kuang M, Wang L, Song Y, 2014, Controllable Printing Droplets for High-Resolution Patterns. *Adv Mater*, 26:6950–8.
https://doi.org/10.1002/adma.201305416

59. Scoutaris N, Ross S, Douroumis D, 2016, Current Trends on Medical and Pharmaceutical Applications of Inkjet Printing Technology. *Pharm Res*, 33:1799–816.
https://doi.org/10.1007/s11095-016-1931-3

60. Negro A, Cherbuin Tm Lutolf MP, 2018, 3D Inkjet Printing of Complex, Cell-Laden Hydrogel Structures. *Sci Rep*, 8:17099.
https://doi.org/10.1038/s41598-018-35504-2

61. Ehtezazi T, Dempster NM, Martin GD, *et al.*, 2014, Development of High-Throughput Glass Inkjet Devices for Pharmaceutical Applications. *J Pharm Sci*, 103:3733–42.
https://doi.org/10.1002/jps.24192

62. Poozesh S, Saito K, Akafuah NK, *et al.*, 2016, Comprehensive Examination of a New Mechanism to Produce Small Droplets in Drop-on-Demand Inkjet Technology. *Appl Phys A*, 122:110.
https://doi.org/10.1007/s00339-016-9630-9

63. Li W, Mille LS, Robledo JA, *et al.*, 2020, Recent Advances in Formulating and Processing Biomaterial Inks for Vat Polymerization-Based 3D Printing. *Adv Healthc Mater*, 9:2000156.
https://doi.org/10.1002/adhm.202000156

64. Ng WL, Lee JM, Zhou M, *et al.*, 2020, Vat Polymerization-Based Bioprinting-Process, Materials, Applications and Regulatory Challenges. *Biofabrication*, 12:022001.
https://doi.org/10.1088/1758-5090/ab6034

65. Melchels FP, Feijen J, Grijpma DW, 2010, A Review on Stereolithography and its Applications in Biomedical Engineering. *Biomaterials*, 31:6121–30.
https://doi.org/10.1016/j.biomaterials.2010.04.050

66. Kumar H, Kim K, 2020, Stereolithography 3D Bioprinting. *Methods Mol Biol*, 2140:93–108.

67. Laza SC, Polo M, Neves AA, *et al.*, 2012, Two-Photon Continuous Flow Lithography. *Adv Mater*, 24:1304–8.
https://doi.org/10.1002/adma.201103357

68. Annabi N, Tamayol A, Uquillas JA, *et al.*, 2014, 25th Anniversary Article: Rational Design and Applications of Hydrogels in Regenerative Medicine. *Adv Mater*, 26:85–123.
https://doi.org/10.1002/adma.201303233

69. Ho CM, Mishra A, Hu K, *et al.*, 2017, Femtosecond-Laser-Based 3D Printing for Tissue Engineering and Cell Biology Applications. *ACS Biomater Sci Eng*, 3:2198–214.
https://doi.org/10.1021/acsbiomaterials.7b00438

70. Gauvin R, Chen YC, Lee JW, *et al.*, 2012, Microfabrication of Complex Porous Tissue Engineering Scaffolds using 3D Projection Stereolithography. *Biomaterials*, 33:3824–34.
https://doi.org/10.1016/j.biomaterials.2012.01.048

71. Kelly BE, Bhattacharya I, 2019, Volumetric Additive Manufacturing Via Tomographic Reconstruction. *Science*, 363:1075–9.

72. Raman R, Bhaduri B, Mir M, *et al.*, 2016, High-Resolution Projection Microstereolithography for Patterning of Neovasculature. *Adv Healthc Mater*, 5:610–9.
https://doi.org/10.1002/adhm.201500721

73. Xu X, Awad A, Robles-Martinez P, *et al.*, 2021, Vat Photopolymerization 3D Printing for Advanced Drug

Delivery and Medical Device Applications. *J Control Release*, 329:743–57.
https://doi.org/10.1016/j.jconrel.2020.10.008

74. Mostafa KG, Arshad M, Ullah A, *et al.*, 2020, Concurrent Modelling and Experimental Investigation of Material Properties and Geometries Produced by Projection Microstereolithography. *Polymers* (*Basel*), 12:506.
https://doi.org/10.3390/polym12030506

75. Ligon SC, Liska R, 2017, Polymers for 3D Printing and Customized Additive Manufacturing. *Chem Rev*, 117:10212–90.
https://doi.org/10.1021/acs.chemrev.7b00074

76. Park JW, Oh SA, Yea JW, *et al.*, 2017, Fabrication of Malleable Three-Dimensional-Printed Customized Bolus Using Three-Dimensional Scanner. *PLoS One*, 12:e0177562.
https://doi.org/10.1371/journal.pone.0177562

77. Kang D, Wang B, Peng Y, *et al.*, 2020, Low-Cost iPhone-Assisted Processing to Obtain Radiotherapy Bolus Using Optical Surface Reconstruction and 3D-Printing. *Sci Rep*, 10:8016.
https://doi.org/10.1038/s41598-020-64967-5

78. Robertson FM, Couper MB, Kinniburgh M, *et al.*, 2021, Ninjaflex vs Superflab: A Comparison of Dosimetric Properties, Conformity to the Skin Surface, Planning Target Volume Coverage and Positional Reproducibility for External Beam Radiotherapy. *J Appl Clin Med Phys*, 22:26–33.
https://doi.org/10.1002/acm2.13147

79. An HJ, Kim MS, Kim J, *et al.*, 2019, Geometric Evaluation of Patient-Specific 3D Bolus from 3D Printed Mold and Casting Method for Radiation Therapy. *Prog Med Phys*, 30:32.
https://doi.org/10.14316/pmp.2019.30.1.32

80. Burleson S, Baker J, Hsia AT, *et al.*, 2015, Use of 3D Printers to Create a Patient-Specific 3D Bolus for External Beam Therapy. *J Appl Clin Med Phys*, 16:5247.

81. Park JM, Son J, An HJ, *et al.*, 2019, Bio-Compatible Patient-Specific Elastic Bolus for Clinical Implementation. *Phys Med Biol*, 64:105006.
https://doi.org/10.1088/1361-6560/ab1c93

82. Park JW, Yea JW, 2016, Three-Dimensional Customized Bolus for Intensity-Modulated Radiotherapy in a Patient with Kimura's Disease Involving the Auricle. *Cancer Radiother*, 20:205–9.
https://doi.org/10.1016/j.canrad.2015.11.003

83. Obeid JP, Gutkin PM, Lewis J, *et al.*, 2019, Volumetric Modulated Arc Therapy and 3-Dimensional Printed Bolus in the Treatment of Refractory Primary Cutaneous Gamma Delta Lymphoma of the Bilateral Legs. *Pract Radiat Oncol*, 9:220–5.
https://doi.org/10.1016/j.prro.2019.02.016

84. Munoz L, Rijken J, Hunter M, *et al.*, 2020, Investigation of Elastomeric Materials for Bolus using Stereolithography Printing Technology in Radiotherapy. *Biomed Phys Eng Express*, 6:045014.
https://doi.org/10.1088/2057-1976/ab9425

85. Tack P, Victor J, Gemmel P, *et al.*, 2016, 3D-Printing Techniques in a Medical Setting: A Systematic Literature Review. *Biomed Eng Online*, 15:115.
https://doi.org/10.1186/s12938-016-0236-4

86. Thrasher CJ, Schwartz JJ, Boydston AJ, 2017, Modular Elastomer Photoresins for Digital Light Processing Additive Manufacturing. *ACS Appl Mater Interfaces*, 9:39708–16.
https://doi.org/10.1021/acsami.7b13909

87. Field J, Haycock JW, Boissonade FM, *et al.*, 2021, A Tuneable, Photocurable, Poly(Caprolactone)-Based Resin for Tissue Engineering-Synthesis, Characterisation and Use in Stereolithography. *Molecules*, 26:1199.
https://doi.org/10.3390/molecules26051199