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REVIEW

Three-dimensional printing: review of application in medicine and hepatic surgery

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ABSTRACT Three-dimensional (3D) printing (3DP) is a rapid prototyping technology that has gained increasing recognition in many different fields. Inherent accuracy and low-cost property enable applicability of 3DP in many areas, such as manufacturing, aerospace, medical, and industrial design. Recently, 3DP has gained considerable attention in the medical field. The image data can be quickly turned into physical objects by using 3DP technology. These objects are being used across a variety of surgical specialties. The shortage of cadaver specimens is a major problem in medical education. However, this concern has been solved with the emergence of 3DP model. Custom-made items can be produced by using 3DP technology. This innovation allows 3DP use in preoperative planning and surgical training. Learning is difficult among medical students because of the complex anatomical structures of the liver. Thus, 3D visualization is a useful tool in anatomy teaching and hepatic surgical training. However, conventional models do not capture haptic qualities. 3DP can produce highly accurate and complex physical models. Many types of human or animal differentiated cells can be printed successfully with the development of 3D bio-printing technology. This progress represents a valuable breakthrough that exhibits many potential uses, such as research on drug metabolism or liver disease mechanism. This technology can also be used to solve shortage of organs for transplant in the future.

KEYWORDS 3D printing technology; 3D bio-printing technology; surgery; education; hepatic surgery

Introduction

Three-dimensional (3D) printing (3DP) is an emerging rapid prototyping method. Also known as additive manufacturing, 3DP is a representative technology of the “third industrial revolution”. Unlike conventional machining that removes material in a subtractive manner, 3DP is a method whereby an actual structure is created by a layering technique using computer-aided design software, which relays the signals to the 3D printer[1]. 3DP involves the conversion of a computerized 3D model into two-dimensional (2D) slices. These slice design files are used to generate solid layers using a range of manufacturing techniques and additive fabrication tools. Finally, the work material is laid down layer by layer, eventually building up a solid model[2]. 3DP allows anyone to rapidly convert digital 3D models into physical components. 3DP has been used in many applications and industries that benefit from the creation of bespoke physical objects, as well as product design and engineering[3].

Of the established rapid prototyping techniques used in the medical arena, five commonly used methods of additive manufacturing are available as follows[4]: stereo lithography, selective laser sintering, fused deposition modeling, laminated object manufacturing, and inkjet printing.

Stereo lithography uses photopolymers that are cured by ultraviolet light. An ultraviolet laser scans a vat of light-curable resin solidifying target areas on the surface of the liquid. The floor of the fluid container gradually descends, thereby increasing the depth of the material as the model grows. Then, successive layers of resin are cured on top of each other.

Selective laser sintering is based on small particles of thermoplastic, metal, ceramic or glass powders that are fused by a high-powered laser. The materials used include nylon or metals, such as titanium or stainless steel. The high-powered laser is used to sweep the powder, tracing out the shape of a 2D slice, and melting and fusing areas of the powder to form the geometry of each layer. A new layer of fresh powder is

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then added and the process is repeated.

In fused-deposition modeling, layers are created by the deposition of a heat-softened polymer with the use of a computer-controlled extrusion nozzle. This technique is most commonly used in most economical consumer printers, but rarely in medical applications.

Laminated object manufacturing uses thin layers of paper or plastic film that are shaped by a laser cutter and glued together.

Inkjet printing is based on different kinds of fine powders, such as plaster or starch. The parts of this layer belonging to the 3D object are bonded by an adhesive liquid deposited by another piston after a layer of the powder has been dispended by a piston. Inkjet printing can also be used to generate a 3D scaffold with different types of tissue by printing living cells and biomaterials simultaneously[5,6].

3D bio-printing technology is a new medical engineering technology. This technology can be defined as a special biological printer as the main means, processing active materials including cells, growth factors, and biological material as the main content, and restoring the body's tissues and organs as the primary goal. 3DP compared with other tissue engineering scaffolds and rapid prototyping technologies exhibits the following advantages: 1) high accuracy: 3D printers can build complex tissues or organs with high accuracy. 3D printers can also assemble and build structures at a cellular level. As a basic unit of the human body, cells range in size from several to tens of micrometers; the resolution of the regulation of the cell distribution should be under 10 μm; however, using traditional tissue engineering technology to achieve such a fine resolution is difficult[7]. 2) good integration: 3DP can integrate the different cells and components of tissues and organs. 3) fast reconstruction: 3D scanners can quickly and controllably reproduce computerized 3D models that include a tissue or organ defect. Then, we can use the acquired clinical imaging data for 3D reconstruction. 4) low cost: The manufacturing process of complex tissues and organs can be personalized. The cost can also be controlled. Multiple patient-specific preoperative physical models have been created using both portal and hepatic venous anatomies from patient data at a cost of less than $100 per model[8]. In traditional manufacturing, the more complex the product structure, the higher the cost. However, no such problem exists with 3DP. Fully customized manufacturing can be produced on demand. In addition, printing a complex structure does not increase additional costs.

Applications of 3DP in medicine

Recently, 3DP has been introduced in the medical domain, following long-standing use in the manufacturing industry. In the last decade, 3DP has been used in a variety of medical applications (e.g., as an educational and training tool and for preoperative planning).

Anatomical models

Educational and training tool

Medical models exhibit a crucial role in teaching basic and clinical medicine. Manufacturing medical models in conventional ways is time consuming, and the process is complex. The costs are also high. With the invention of 3DP by Charles W. Hull in the early 1980s, producing physical objects from digital files became possible[9]. 3DP can produce accurate reproductions of anatomical structures at a relatively low cost that can reveal normal or pathological variations[7,10]. 3D prints of anatomical structures can be produced with high accuracy compared with the original specimens[7,11]. 3DP has facilitated the quick fabrication of accurate physical models. The internal organ or tissue structure details can be displayed realistically using these models. Thus, students' medical knowledge is quickly improved. Preece et al.[12] showed improvements in student scores on anatomical tests by using 3D-printed models to teach equine limb anatomy. Additionally, 3DP in the field of surgery can be used in both surgical training and practice to improve the experience of surgeons. Surgical training is very

Table 1 Different types of 3DP technology

Types of 3DP technology	Advantages	Disadvantages	Cost
Stereo lithography	High-resolution	Needs post-curing	++
Selective laser sintering	High-productivity	Rough surface, high-cost	+++
Fused deposition modeling	Low-cost	Low accuracy, time-consuming	+
Laminated object manufacturing	Fast production time	Limited material	+
Inkjet printing techniques	High-precision	Needs post-curing	+

important for young surgeons, and the cadaver model is the gold standard in developing surgical skills[13]. However, the efficiency of this model is greatly reduced because using cadavers is limited by issues related to cost, reproducibility, and procurement[14]. Furthermore, repeated use of a cadaver can also destroy the normal anatomy[13].

A 3D-printed model can allow a young doctor to bypass the limitations of the cadaver model. This model can also help them to fully understand the anatomical structures of tissues and the procedures of surgical operations. In a study on a randomized controlled trial comparing 3D prints versus cadaveric materials for learning external cardiac anatomy, Lim et al[15]. divided students into three groups as follows: one learned 3D-printed materials, one learned from cadavers, and the final one learned from the combination of the two. The study suggested that reliance on 3D prints showed no disadvantages among students in learning anatomy. 3D-printed models can provide solutions to the difficulties that educators encounter when they use traditional methods. Costello et al.[16] obtained five common ventricular septal defect (VSD) subtypes via magnetic resonance imaging (MRI). The images were segmented and built into 3D computer-aided design models using software. Then, they used a 3D printer to print a high-fidelity heart model for each VSD subtype. Thereafter, a medical course using these heart models was developed and implemented in the instruction of 29 medical students. Following instruction with these high-fidelity models, Costello et al.[16] found that all students achieved significant improvement in knowledge acquisition ($P < 0.0001$), knowledge reporting ($P < 0.0001$), and structural conceptualization ($P < 0.0001$) of VSDs. This kind of innovative, simulation-based educational approach can create a novel opportunity to stimulate students' interests in different fields. The cost of 3D printers continues to decrease because of increasing competition and market pressures. In addition, the day is approaching when 3D printers will become widely available in medical schools. Thus, anatomical models will be produced at a significantly low cost using low resolutions and cheap materials coupled with minimal post-printing processing, but still providing the necessary information for surgical education and patient communication[17].

Preoperative planning

Complex surgery always needs preoperative evaluation and practice to ensure success. Doctors can reconstruct computed tomography (CT) or MRI medical image data using computer software. Doctors can also print out a 3D model of the part of the patient's body that needs surgery using a 3D printer. Then, doctors can design the patient's preoperative surgery process and personalize their postoperative treatment based on these 3D-printed models. This technology has been used in various fields, including neurosurgery[18], plastic surgery[19], oral and maxillofacial surgery[20], orthopedics[21], and organ transplantation[22]. 3DP increases the accuracy of preoperative planning because it can reproduce the structures of normal tissues and pathological structures accurately.

Preoperative planning in neurosurgery is imperative as the operation requires high accuracy. 3D-printed models are effective tools in constructing a preoperative plan. For example, Spottiswoode et al.[18] printed a 3D model based on MRI data acquired before surgery to treat two patients with lesions in the proximity of the motor cortex. The 3D models provided the surgeons additional information on the entry point that helped them avoid damage to areas of eloquent cortex. Moreover, the model showed a clear view of both the depth and extent of the tumor. Condino et al.[23] printed an abdominal cavity that was similar to the patient's anatomy based on imaging. Markert[24] used 3DP to create an organ model to construct a surgical plan before the operation. Obtaining information on defects and anatomical relationships before plastic surgery operations is important. An 82-year-old patient underwent ankle replacement surgery complicated by wound dehiscence, infection, and presentation of exposed prosthesis. After debridement failure, the doctors planned to use soft tissue to cover the dead space, filling and reconstructing it with the radial forearm free flap. The surgeons obtained imaging data via CT scan. Then, a 3D model was printed. The model enhanced the surgeons' understanding of the defect morphology. Daniel et al.[19] performed a study among 10 patients who planned to undergo osteoplastic flap surgery. They used a 3D-printed model to cover the frontal sinus. An adjacent area was then created using CT images with frontal sinus margins at an accuracy of up to 5 mm range maximum. This method was consistently accurate with an osteoplastic flap margin within 1 mm of the actual frontal sinus margin, although no data were available for comparison with current mapping modalities.

Using 3D-printed models is more precise than using 2D images[19]. Doctors can practice the steps of complex operations repeatedly by using 3D-printed models that can help surgeons foresee intraoperative complications[25]. At the same time, skilled operation during surgery can shorten the time of surgery and anesthesia. The rate and probability of complications are reduced as well. The use ratio of 3DP for surgical planning has not changed significantly because the standard methods of preoperative plans are sufficient. Short surgery time and high surgical success rate can be achieved although additional costs are associated with using 3DP to construct preoperative plans. However, the time taken to produce a 3D model also means that it cannot be used in every kind of surgery. Thus, this model is unsuitable particularly during emergency cases.

Surgical instruments

Prosthesis quality is a global problem because of the high manufacturing costs and complicated manufacturing process. 3DP is widely used in the prosthesis manufacturing field. Besides the use of cost-effective materials, 3DP allows rapid prototyping that can reduce the production time and cost significantly; as a result, 3DP provides an effective solution for prosthesis development[26]. 3D-printed medical implants can fit well the human body, thereby improving the treatment effect. Ciocca describes personalized bone plates with porous structures made by laser sintering of titanium powder. These plates were used in the transplantation of a fibula flap to a patient with a mandibular defect. The advantages of this method include avoiding repeated modification of the titanium plate during the operation. Thus, the chance of titanium plate looseness or breakage after the operation is reduced. This effect can also maximize the restoration of mandibular appearance; the duration of surgery and the chance of postoperative complications are also reduced[27]. Zopf et al.[28] implanted a customized, bioresorbable tracheal splint to an infant with tracheo-bronchomalacia. The implant was designed based on a CT image of the patient's airway. Then, the design was 3D printed. Bronchoscopy revealed normal patency of the bronchus without dynamic collapse after the operation; no complications were observed one year after stent implantation. A digital nose database was developed at the University Hospital Dresden and has proven to be a useful tool to provide patients with nasal prostheses based on 3DP technology[29]. This method is different from conventional processes because of the elimination of physical modeling. As a result, strain on the patient is reduced.

A high prosthesis acceptance rate can be achieved by early integration of the patient in the selection and decision-making processes. The time required for the fabrication process can also be reduced[29]. 3DP has also been used widely in plastic and reconstructive surgery. Human skin is composed of an integrated network of sensors that relay information on tactile and thermal stimuli to the brain. This condition allows us to maneuver within our environment safely and effectively. Electronic skins (e-skin) are already capable of providing augmented performance over their organic counterparts both in terms of superior spatial resolution and thermal sensitivity. Fully integrated e-skin is expected to be possible in the future[30]. The models can also improve communication with the patient. Several studies have been published on these topics, including using 3DP for foot and ankle surgery, congenital heart disease treatment, shoulder replacement, repair of jaw defects, total hip replacement, spinal implants, and skull reconstruction. The technology provides a powerful boost to human medical development.

Bio-printing

Since 2000, more than 30 different types of mature differentiated cells of human or animals have been printed successfully. The sources of these cells vary widely. These sources include the nerves, heart, liver, skin, muscles, bones, kidneys, pancreas, or retina. The major obstacles to bio-printing that need to be solved are the twin problems of cell migration and differentiation. In 2007, Wake Forest Regeneration Medical Center in the United States was the first to print stem cells. The institution used a 3D inkjet printer to print human amniotic fluid stem cells, and successfully differentiated functional bone tissue; the resulting bone tissue exhibited high density and strength[31]. The ultimate goal of bio-printing technology is to print organs and tissues that are patient specific and can be directly implanted into patients. Bio-printing is also used in cardiothoracic surgery. For example, Duan et al.[32,33] used the technology to produce heart valves. They isolated valve interstitial cells and smooth muscle cells. These cells were separately mixed with hydrogel materials and directly printed into a heterogeneous 3D aortic valve construct. Fine-tuning materials for valves was necessary. The team looked further into manipulating the hydrogel materials using methacrylated hyaluronic acid and methacrylated gelatin. The materials showed good cell viability and tensile biomechanics during initial testing; however, long-term studies are needed to show that their properties are adequately maintained[32,33]. In recent years, breakthroughs in bio-printing have been obtained in many fields, such as in blood vessels[34], the skin[35], spine cartilage[36], and the liver[37]. This development has excited many researchers in the medical field. However, bio-printing as an evolving technology is still in its infancy[38].

Applications of 3DP in hepatic surgery

Two main applications have been found in the field of hepatic surgery with the advancement of 3DP, according to previously published research. One involves teaching or surgical plan formulation using resin material to manufacture a liver structure model. The other involves printing functional liver cells via bio-printing technology that can be used in the study of liver disease and drug research.

3D-printed liver model

Liver resection is the only successful treatment available for liver cancer. In liver resection, precisely locating the blood vessels in the liver, bile duct, and tumor is imperative. The conventional method uses a preoperative CT or MRI to estimate the location of the lesion and the positional relationship between the tumor and important blood vessels. Doctors can then decide the best operative approach and specific solutions. However, 2D images in some complicated cases cannot offer an accurate preoperative view. As a result, the position of some important vascular structures is unclear. This condition can also increase the risk associated with the operation. 3DP plays an important role in positioning the relationship between the important vasculature and the lesions. 3DP can create a transparent 3D model allowing the surgeon to be released from an "imagined" dilemma. Doctors can foresee the intraoperative situation clearly, determine the paths of important pipes, and even practice the operation. 3DP can improve the success rate of operations and decrease the rate of surgical risks.

For example, Igami et al.[39] used a 3D-printed liver model for hepatectomy in two patients diagnosed with synchronous multiple liver metastases from colorectal cancer. One of the tumors shrank and was not visible by ultrasonography as they underwent chemotherapy before surgery. Following 3D fusion images, the resection line was found easily and clearly. Then, the team converted image information into a 3D-printed liver model. The team also planned the appropriate hepatectomy for each patient. Finally, the team completed the operation precisely with negative cut edges. The authors pointed out that different doctors have different 2D display understandings of the spatial relationship between blood vessels and tumors. However, the understanding of the spatial relationship is completely consistent when the 3D-printed liver model is used. Similarly, Souzaki et al.[40] reported the case of a three-year-old girl with a PRETEXT IV liver tumor. Tumor size was reduced after neoadjuvant chemotherapy. However, the tumor was still difficult to remove because it was in the portal site. Although chemotherapy is usually effective for hepatoblastoma (HB), complete resection is the most important prognostic factor in achieving a cure for HB[41]. Thus, preoperative planning was important for this patient. The team produced a 3D-printed liver model to understand clearly the patient's anatomy. This model was used to visualize complex structures, such as the portal vein, hepatic vein, and tumor, based on preoperative CT images. Eventually, the patient accepted a successful left hepatic lobe resection[40].

Xiang et al.[42] used 3DP to successfully diagnose and operate a complex massive hepatocellular carcinoma. The tumor with rare variations of hepatic artery and portal vein was previously misdiagnosed and even mistreated because of inaccessibility to advanced technology. Enhanced CT data were collected. Then, the team imported the CT image data to the Medical Imaging Three Divisional Visualization System to obtain 3D visualization models of the liver, lesion, arterial system in the abdomen, and portal and hepatic veins. Eventually, the data were transformed into a 3D-printed model. Using 3D visualization analysis, the clinicians found rare variations in the abdominal blood vessels as follows: the segment 4 portal vein was absent, and variant segment 4 portal vein originated from the right anterior portal vein. The team designed a preoperative surgical plan following the relationship between the tumor and the portal vein variation in the 3D-printed model. Finally, the actual surgical procedure was consistent with the preoperative surgical plan. The operation was also successful. Several articles on liver resection surgery using 3DP have been reported. In addition, the authors agree that doctors can communicate with patients to help them understand their liver tumor diseases using a preoperative 3D-printed model. This method also helps young doctors to study liver tumor diseases, thereby shortening their learning curve. This method also enables precise liver tumor resection to improve patient prognosis.

3D-printed models also play an important role in liver transplantation. As the demand for liver transplants has increased, supply of cadaveric livers becomes short, leading to increased demand for living donor liver transplantation[43]. Living donors are healthy individuals. Thus, ensuring their safety is important. Zein et al.[22] printed translucent 3D models of the livers of three donors and three receptors. They used these models for preoperative planning and intraoperative guidance. They believed that 3D organ printing is an important tool that enables surgeons to clearly see the spatial relationships between the vascular and biliary anatomical structures. Then, surgery is ultimately facilitated, potentially decreasing the rate of complications. Zein et al.[22] found that these models exhibit high accuracy with average dimensional errors of less than 4 mm for the entire model and less than 1.3 mm for vascular diameters (the portal vein and its main branches, the hepatic veins, and the hepatic artery). A physical 3D-printed model can improve the perceived tactile and spatial relationship of the liver vasculature precisely compared with a 3D computerized graphics model. This method can reduce the potential complications of surgery. Thus, patient prognosis is improved. In addition, synchronous adjustment of the 3D-printed liver model during dissection of the hepatic portal can help the surgeon to quickly identify and locate the key anatomical site. 3D-printed models can shorten operation time and cold ischemia time in liver transplantation surgery by providing information on the liver space configuration. The accuracy of 3DP as a tool for constructing a preoperative plan is higher than that of conventional and 3D imaging.

3D bio-printed livers

The shortage of organs has become a global problem. For a long time, the medical industry has invested substantial resources into research to solve inadequacy of organs for transplant. 3D bio-printing is a promising development.

Ott et al.[44] found that organs with cell-free processing can be used as a scaffold. Ott implanted new myocardial cells and rat arterial endothelial cells in a treated heart following the premise of preserving the original native vascular network of the rat, as well as cell-free processing. The new myocardial cells produced contractions after cultivation. The heart started beating as well. Liver transplantation is the only available treatment for severe liver failure. However, it is limited by organ shortages. The liver possesses a complex microarchitecture consisting of hepatocytes and supporting cells organized into 3D hexagonal lobules. Hepatocytes lose some functions in 2D cell cultures because of the conditions of this special structure. Therefore, the emergence of 3DP enables the possibility to produce an optimal survival environment for hepatocytes. In recent years, the concept of a liver-on-a-chip has received significant attention[45]. New drugs sometimes fail in clinical trials because of hepatotoxicity, which is not predicted by animal models. With the help of a mini-liver, we can directly obtain data concerning these drugs to avoid failure in clinical trials[46]. Uygun et al.[47] demonstrated a novel approach to generate transplantable liver grafts using a decellularized liver matrix. The recellularized graft supports liver-specific functions, such as albumin secretion, urea synthesis, and cytochrome P450 (CYP) expression at comparable levels to a normal liver *in vitro*. In addition, the researchers transplanted recellularized liver grafts into rats. They found that these grafts can support hepatocyte survival and function with minimal ischemic damage. The results provided a proof of principle for the generation of a transplantable liver graft as a potential treatment for liver disease. The cell-free scaffold is also used in lung research[47]. The possibility of an organ being cultivated *in vitro* may bear fruit through 3D printing of a biological scaffold and cell cultivation on the scaffolds. Researchers have planted immature liver cells and alveolar epithelial cells on such scaffolds, and obtained the corresponding organs[47,48].

According to media reports, a company in the United States used a 3D printer to print out mini-liver cells (depth: 0.5 mm, width: 4 mm). These cells were capable of some real liver functions, including producing albumin and CYP. However, peer-reviewed publication is yet to be reported on these data. Thus, the results remain to be clarified.

The Mechanics Department of Tsinghua University currently works with the Hepatic Surgery Department of Peking Union Medical College Hospital. The department prints human liver tissue of up to 1 cm wide and 0.5 cm thick using technology based on that used to print liver tissue in mice (**Figure 1**). The structure exhibits a long-term survival rate of more than 28 days. The structure maintains a specified albumin secretion rate and CYP enzyme activity. An obvious biliary tree structure has also been set up by this structure. These cells exhibit more advantages in terms of liver function than existing liver cells that are cultivated in 2D style *in vitro* that last only for two to three days. Under the stimulus of drugs, CYP enzyme activity, the expression quantity of protein, and the amount of mRNA expression of structure are significantly increased. Glutathione S-

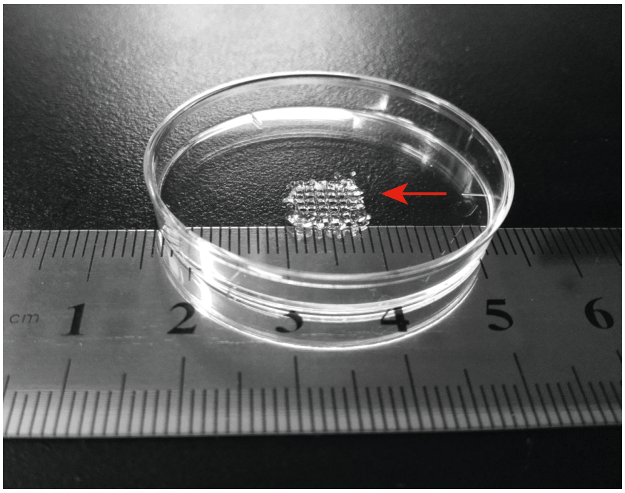

Figure 1 Bio-printing liver (indicated by an arrow) made by the Mechanics Department of Tsinghua University and the Hepatic Surgery Department of Peking Union Medical College Hospital.

transferase and the expression of aromatic hydrocarbon receptor also increased accordingly. These data show that the model simulates the human liver detoxification function in the body that can be used for research on drug metabolism and liver disease mechanisms. The study results have been published and the findings represent a first step in 3D printing of living liver organs.

3DP technology is developing rapidly in liver surgery with a considerable prospect. However, this technology exhibits disadvantages and limitations. 3D-printed models are reliant on imaging. Accordingly, these models will be prone to imaging errors. Imaging accuracy thus needs to be improved to ensure the high accuracy of 3D-printed models. 3D model cannot be used in emergency cases, such as hepatic rupture, because of the time needed to produce this model. Although researchers have printed functional liver tissue, 3D-printed models cannot replace normal liver in the organism. With the development of 3DP, 3DP can be used in hepatic surgery widely. Shortage of inadequate organs for transplant can be solved as well.

Conclusions

3DP has brought a new era of medical research and applications. 3DP has also created many exciting results in many fields. 3DP is a tool that can aid in many different ways and add value in the field of surgery. 3DP benefits include surgical planning, medical education, patient education, implants, prosthetics, and other applications. The application of 3DP exhibits broad appeal and potential applications in hepatic surgery. However, 3DP has still some limitations, such as cost, accuracy, and the size of models. The main costs involve hardware, software, and printing materials. The largest part of investment is software and hardware. Clinicians in some developing countries cannot afford 3DP cost. The accuracy of 3DP as a tool to construct a preoperative plan is higher than that of conventional 3D imaging. However, 3DP accuracy is reliant on the underlying 2D imaging data. Therefore, the accuracy and processing technology of 2D images still need to be improved. Currently, 3DP can only be applied to structures that do not exceed certain dimensions because 3D printers are unable to produce extremely large parts, e.g., an entire human body. Printing time depends on the size and complexity of the models[49]. The time to produce objects involved should also be considered. The time of imaging and data processing decreased to minutes with the development of imaging software. In addition, for the actual printing of the object, many teams are able to perform this process within 24 h[50-52]. However, time needed to produce a 3D model also means that it can only be used in surgery in elective cases. Thus, 3DP is unsuitable for some emergency cases.

However, some of these limitations can be overcomed by future technological developments. The limitation of model size can be overcomed by dividing the models into small parts, then combining them after printing or by producing a miniature version of large structures via post-processing. Moreover, the cost of time and money may also decrease with the development of software and hardware of 3DP technology. 3DP is likely to change the healthcare industry greatly in the future. CT, MRI, and some conventional techniques cannot be entirely replaced. However, 3D models enable surgeons to perform a hands-on simulation before the operation and construct a comprehensive operative plan in the absence of a time-pressured surgical environment. We believe that 3DP will be widely applied in clinical settings. 3DP may one day achieve the goal of whole organs being printed for use in transplants. 3D-printed living liver tissue will gradually play an important role in the study of the liver. 3DP can also provide a powerful boost to the development of medicine. The current surgical uses of 3DP are in their infancy with varying levels of uptake across different specialties. However, we believe that 3DP possesses the potential to revolutionize human life in the future. 3DP is significantly effective in the medicine field.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

References

1. Cohen A, Laviv A, Berman P, Nashef R, Abu-Tair J. Mandibular reconstruction using stereolithographic 3-dimensional printing modeling technology. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 108: 661–6.
2. Derby B. Printing and prototyping of tissues and scaffolds. Science. 2012; 338: 921–6.
3. Sachs E, Cima M, Cornie J, Brancazio D, Bredt J, Curodeau A, et al. Three-dimensional printing: the physics and implications of additive manufacturing. CIRP Ann - Manuf Techn. 1993; 42: 257–60.

4. AlAli AB, Griffin MF, Butler PE. Three-dimensional printing surgical applications. Eplasty. 2015; 15: e37.
5. Campbell PG, Weiss LE. Tissue engineering with the aid of inkjet printers. Expert Opin Biol Ther. 2007; 7: 1123–7.
6. Boland T, Xu T, Damon B, Cui X. Application of inkjet printing to tissue engineering. Biotechnol J. 2006; 1: 910–7.
7. McMenamin PG, Quayle MR, McHenry CR, Adams JW. The production of anatomical teaching resources using three-dimensional (3D) printing technology. Anat Sci Educ. 2014; 7: 479–86.
8. Watson RA. A low-cost surgical application of additive fabrication. J Surg Educ. 2014; 71: 14–7.
9. Hull CW. Apparatus for production of three-dimensional objects by stereolithography. US Patent 4575330 A, 1986.
10. AbouHashem Y, Dayal M, Savanah S, Štrkalj G. The application of 3D printing in anatomy education. Med Educ Online. 2015; 20: 29847.
11. Adams JW, Paxton L, Dawes K, Burlak K, Quayle M, McMenamin PG. 3D printed reproductions of orbital dissections: a novel mode of visualising anatomy for trainees in ophthalmology or optometry. Br J Ophthalmol. 2015; 99: 1162–7.
12. Preece D, Williams SB, Lam R, Weller R. "Let's get physical": advantages of a physical model over 3D computer models and textbooks in learning imaging anatomy. Anat Sci Educ. 2013; 6: 216–24.
13. Blaschko SD, Brooks HM, Dhuy SM, Charest-Shell C, Clayman RV, McDougall EM. Coordinated multiple cadaver use for minimally invasive surgical training. JSLS. 2007; 11: 403–7.
14. Waran V, Narayanan V, Karuppiah R, Pancharatnam D, Chandran H, Raman R, et al. Injecting realism in surgical training-initial simulation experience with custom 3D models. J Surg Educ. 2014; 71: 193–7.
15. Lim KH, Loo ZY, Goldie SJ, Adams JW, McMenamin PG. Use of 3D printed models in medical education: a randomized control trial comparing 3D prints versus cadaveric materials for learning external cardiac anatomy. Anat Sci Educ. 2016; 9: 213–21.
16. Costello JP, Olivieri LJ, Krieger A, Thabit O, Marshall MB, Yoo SJ, et al. Utilizing three-dimensional printing technology to assess the feasibility of high-fidelity synthetic ventricular septal defect models for simulation in medical education. World J Pediatr Congenit Heart Surg. 2014; 5: 421–6.
17. Jones DB, Sung R, Weinberg C, Korelitz T, Andrews R. Three-dimensional modeling may improve surgical education and clinical practice. Surg Innov. 2016; 23: 189–95.
18. Spottiswoode BS, van den Heever DJ, Chang Y, Engelhardt S, Du Plessis S, Nicolls F, et al. Preoperative three-dimensional model creation of magnetic resonance brain images as a tool to assist neurosurgical planning. Stereotact Funct Neurosurg. 2013; 91: 162–9.
19. Daniel M, Watson J, Hoskison E, Sama A. Frontal sinus models and onlay templates in osteoplastic flap surgery. J Laryngol Otol. 2011; 125: 82–5.
20. Ayoub AF, Rehab M, O'Neil M, Khambay B, Ju X, Barbenel J, et al. A novel approach for planning orthognathic surgery: the integration of dental casts into three-dimensional printed mandibular models. Int J Oral Maxillofac Surg. 2014; 43: 454–9.
21. Giovinco NA, Dunn SP, Dowling L, Smith C, Trowell L, Ruch JA, et al. A novel combination of printed 3-dimensional anatomic templates and computer-assisted surgical simulation for virtual preoperative planning in charcot foot reconstruction. J Foot Ankle Surg. 2012; 51: 387–93.
22. Zein NN, Hanouneh IA, Bishop PD, Samaan M, Eghtesad B, Quintini C, et al. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. Liver Transpl. 2013; 19: 1304–10.
23. Condino S, Carbone M, Ferrari V, Faggioni L, Peri A, Ferrari M, et al. How to build patient-specific synthetic abdominal anatomies. An innovative approach from physical toward hybrid surgical simulators. Int J Med Robot. 2011; 7: 202–13.
24. Markert M, Weber S, Lueth TC. A beating heart model 3D printed from specific patient data. Conf Proc IEEE Eng Med Biol Soc. 2007; 2007: 4472–5.
25. Mavili ME, Canter HI, Saglam-Aydinatay B, Kamaci S, Kocadereli I. Use of three-dimensional medical modeling methods for precise planning of orthognathic surgery. J Craniofac Surg. 2007; 18: 740–7.
26. Silva K, Rand S, Cancel D, Chen Y, Kathirithamby R, Stern M. Three-dimensional (3-D) printing: a cost-effective solution for improving global accessibility to prostheses. PM R. 2015; 7: 1312–4.
27. Ciocca L, Mazzoni S, Fantini M, Persiani F, Marchetti C, Scotti R. CAD/CAM guided secondary mandibular reconstruction of a discontinuity defect after ablative cancer surgery. J Craniomaxillofac Surg. 2012; 40: e511–5.
28. Zopf DA, Hollister SJ, Nelson ME, Ohye RG, Green GE. Bioresorbable airway splint created with a three-dimensional printer. N Engl J Med. 2013; 368: 2043–5.
29. Reitemeier B, Götzel B, Schöne C, Stockmann F, Müller R, Lexmann J, et al. Creation and utilization of a digital database for nasal prosthesis models. Onkologie. 2013; 36: 7–11.
30. Hammock ML, Chortos A, Tee BCK, Tok JBH, Bao Z. 25th anniversary article: the evolution of electronic skin (E-Skin): A brief history, design considerations, and recent progress. Adv Mater. 2013; 25: 5997–6038.
31. De Coppi P, Bartsch G Jr, Siddiqui MM, Xu T, Santos CC, Perin L, et al. Isolation of amniotic stem cell lines with potential for therapy. Nat Biotechnol. 2007; 25: 100–6.
32. Duan B, Hockaday LA, Kang KH, Butcher JT. 3D bioprinting of heterogeneous aortic valve conduits with alginate/gelatin hydrogels. J Biomed Mater Res A. 2013; 101: 1255–64.
33. Duan B, Kapetanovic E, Hockaday LA, Butcher JT. Three-dimensional printed trileaflet valve conduits using biological hydrogels and human valve interstitial cells. Acta Biomater. 2014; 10: 1836–46.
34. Nahmias Y, Schwartz RE, Hu WS, Verfaillie CM, Odde DJ. Endothelium-mediated hepatocyte recruitment in the

establishment of liver-like tissue in vitro. Tissue Eng. 2006; 12: 1627–38.

35. Nahmias Y, Arneja A, Tower TT, Renn MJ, Odde DJ. Cell patterning on biological gels via cell spraying through a mask. Tissue Eng. 2005; 11: 701–8.
36. Chen H, Wu D, Yang H, Guo K. Clinical use of 3D printing guide plate in posterior lumbar pedicle screw fixation. Med Sci Monit. 2015; 21: 3948–54.
37. Wang X, Yu X, Yan Y, Zhang R. Liver tissue responses to gelatin and gelatin/chitosan gels. J Biomed Mater Res A. 2008; 87: 62–8.
38. Gerstle TL, Ibrahim AM, Kim PS, Lee BT, Lin SJ. A plastic surgery application in evolution: three-dimensional printing. Plast Reconstr Surg. 2014; 133: 446–51.
39. Igami T, Nakamura Y, Hirose T, Ebata T, Yokoyama Y, Sugawara G, et al. Application of a three-dimensional print of a liver in hepatectomy for small tumors invisible by intraoperative ultrasonography: preliminary experience. World J Surg. 2014; 38: 3163–6.
40. Souzaki R, Kinoshita Y, Ieiri S, Hayashida M, Koga Y, Shirabe K, et al. Three-dimensional liver model based on preoperative CT images as a tool to assist in surgical planning for hepatoblastoma in a child. Pediatr Surg Int. 2015; 31: 593–6.
41. Hishiki T, Matsunaga T, Sasaki F, Yano M, Ida K, Horie H, et al. Outcome of hepatoblastomas treated using the japanese study group for pediatric liver tumor (JPLT) protocol-2: report from the JPLT. Pediatr Surg Int. 2011; 27: 1–8.
42. Xiang N, Fang C, Fan Y, Yang J, Zeng N, Liu J, et al. Application of liver three-dimensional printing in hepatectomy for complex massive hepatocarcinoma with rare variations of portal vein: preliminary experience. Int J Clin Exp Med. 2015; 8: 18873–8.
43. Renz JF, Busuttil RW. Adult-to-adult living-donor liver transplantation: a critical analysis. Semin Liver Dis. 2000; 20: 411–24.
44. Ott HC, Matthiesen TS, Goh SK, Black LD, Kren SM, Netoff TI, et al. Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. Nat Med. 2008; 14: 213–21.
45. Yoon No D, Lee KH, Lee J, Lee SH. 3D liver models on a microplatform: well-defined culture, engineering of liver tissue and liver-on-a-chip. Lab Chip. 2015; 15: 3822–37.
46. Griffith LG, Swartz MA. Capturing complex 3D tissue physiology in vitro. Nat Rev Mol Cell Biol. 2006; 7: 211–24.
47. Uygun BE, Soto-Gutierrez A, Yagi H, Izamis ML, Guzzardi MA, Shulman C, et al. Organ reengineering through development of a transplantable recellularized liver graft using decellularized liver matrix. Nat Med. 2010; 16: 814–20.
48. Ott HC, Clippinger B, Conrad C, Schuetz C, Pomerantseva I, Ikonomou L, et al. Regeneration and orthotopic transplantation of a bioartificial lung. Nat Med. 2010; 16: 927–33.
49. Rengier F, Mehndiratta A, von Tengg-Kobligk H, Zechmann CM, Unterhinninghofen R, Kauczor HU, et al. 3D printing based on imaging data: review of medical applications. Int J Comput Assist Radiol Surg. 2010; 5: 335–41.
50. Tam MD, Laycock SD, Bell D, Chojnowski A. 3-D printout of a dicom file to aid surgical planning in a 6 year old patient with a large scapular osteochondroma complicating congenital diaphyseal aclasia. J Radiol Case Rep. 2012; 6: 31–7.
51. Birnbaum K, Schkommodau E, Decker N, Prescher A, Klapper U, Radermacher K. Computer-assisted orthopedic surgery with individual templates and comparison to conventional operation method. Spine (Phila Pa 1976). 2001; 26: 365–70.
52. Torres K, Staśkiewicz G, Śnieżyński M, Drop A, Maciejewski R. Application of rapid prototyping techniques for modelling of anatomical structures in medical training and education. Folia Morphol (Warsz). 2011; 70: 1–4.

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