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Research Progress and Challenges Analysis of 4D Printing Technology in the Treatment of Esophageal Diseases

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Abstract: 4D printing technology is an important extension of 3D printing technology. After introducing the time dimension, the printed structure can undergo dynamic changes in response to external stimuli such as temperature, pH value, and magnetic field, providing new possibilities for personalized treatment of esophageal diseases. Therefore, this article reviews the research progress of 4D printing technology in the treatment of diseases such as esophageal stenosis, esophagotracheal fistula, and radiation esophagitis. It focuses on analyzing its application potential in fields such as stent design, drug delivery, and tissue engineering, and discusses the challenges faced by 4D printing technology in aspects, such as material selection, printing accuracy, biocompatibility, and clinical transformation. The future development direction was projected.
Keywords: 4D printing; Esophageal diseases; Intelligent materials; Organizational Engineering

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1. Introduction

Esophageal diseases mainly include gastroesophageal reflux disease (GERD), Barrett's esophagus, and esophageal cancer. GERD is a benign esophageal disease. Epidemiological data show that the prevalence of GERD is on the rise worldwide, and the prevalence of GERD in China is as high as 1.9–7.0%. Esophageal cancer is the seventh most common cancer in the world and the sixth leading cause of cancer-related deaths. In 2020, the incidence rate of esophageal cancer in China was 13.80 per 100,000 people, ranking 6th, and the fatality rate was 12.70 per 100,000 people, ranking 4th. It is one of the major malignant tumors threatening the lives and health of the nation [1]. In clinical practice, surgical methods are often adopted to treat esophageal diseases. This traditional approach is often accompanied by significant trauma, a long recovery time for patients after surgery, and may cause various complications. Although endoscopic stent placement can alleviate symptoms to a certain extent, there are also problems such as stent displacement and restenosis. These traditional methods also have obvious deficiencies in terms of personalization and are difficult to precisely meet the unique physiological and pathological needs of each patient. To fully simulate the dynamic healing and regeneration process of human tissues, researchers have proposed the concept of 4D printing, which is expected to provide a possible solution to its static limitations. That is, "smart materials" are prepared into primary structure products through 3D printing technology. 3D printing refers to the process where, under computer-aided control, The process of manufacturing three-dimensional solid objects by means of spraying, extrusion, melting, light curing, etc. Unlike the traditional subtractive forming and assembly processing mode, 3D printing adopts a layer-by-layer additive manufacturing method, which can fold, bend, expand, or contract according to the pre-designed shape under specific conditions and form the final structure [2]. In recent years, the application of 4D printing technology in the treatment of esophageal diseases has gradually attracted the attention of many researchers. However, the related research is still in its infancy at present, and there are still many problems to be deeply explored and solved. This article will systematically review the research progress and challenges of 4D printing technology in the treatment of esophageal diseases, providing useful references for subsequent research.

2. Overview of 4D printing technology

2.1. Definition and principle of 4D printing

4D printing can be simply understood as the organic combination of "3D printing + time". The core essence lies in that through the meticulous design of intelligent materials and the continuous optimization of printing strategies, the printing structure is endowed with the ability to undergo dynamic changes in form, performance, or function under preset external stimulus conditions [3]. The realization of 4D printing cannot do without the following key elements.

2.1.1. Smart materials

This is the material basis of 4D printing. Common smart materials include shape memory polymers (SMP), hydrogels, and shape memory alloys (SMA). These materials possess unique properties and can sensitively respond to external stimuli such as temperature, humidity, pH value, and magnetic fields [4]. For example, shape memory polymers can quickly return to the pre-set shape when stimulated by a specific temperature. Hydrogels can undergo changes such as volume expansion or contraction in response to variations in the humidity or pH value of the surrounding environment.

2.1.2. Stimulus conditions

It is necessary to precisely select the appropriate external stimuli based on the characteristics of the selected intelligent materials. In medical application scenarios, these stimuli often originate from the body's own physiological environment. Take body temperature as an example. Many 4D printed medical devices based on shape memory polymers use the body temperature of around 37℃ as the stimulus source to cause the expected morphological changes within the body.

2.1.3. Mathematical model and printing strategy

With the aid of advanced computer technology means such as Computer-aided Design (CAD) and finite element Analysis (FEA), the dynamic behavior of the printed structure is accurately predicted. Through the simulation analysis of different parameters and the optimization of the printing path, the final printed structure can undergo dynamic changes in the expected way under the set stimulus conditions [5].

3. The application potential of 4D printing in the medical field

4D printing technology, with its unique advantages, has shown broad application prospects in the medical field, mainly reflected in the following aspects.

3.1. Intelligent medical devices

It can be used to manufacture medical devices that can adapt to the shape of human organs, especially stents that can adapt to the shape of blood vessels. They can adjust their own shape within the blood vessels along with the natural dilation and contraction of the blood vessels, reducing mechanical damage to the vessel walls. There are also degradable suturing devices. After the wound heals, they can degrade by themselves under specific stimuli, avoiding the pain caused by the removal of the suturing device during a second operation for the patient [6].

3.2. Drug delivery system

The precise release of drugs can be achieved by constructing drug delivery systems using stimulus-responsive materials. For instance, materials sensitive to the microenvironment of specific disease sites can be designed to encapsulate drugs within them. When the drug delivery system reaches the disease site, under the stimulation of a specific microenvironment, the material changes and precisely releases the drug, enhancing the therapeutic effect of the drug and reducing its toxic and side effects on normal tissues [7].

3.3. Organization engineering

It is possible to construct tissue engineering scaffolds with dynamic bionic structures, providing a more suitable microenvironment for cell growth, proliferation and differentiation, and promoting tissue regeneration. Taking the mechanical environment of human tissues under physiological conditions as an example, this process can print out scaffolds with dynamic mechanical property changes, which is more in line with the actual growth needs of tissues [8].

4. Research progress of 4D printing in the treatment of esophageal diseases

4.1. Personalized stent treatment for esophageal stenosis

The esophagus has a tubular structure. When benign or malignant lesions or significant injuries occur in the esophagus, stenosis is prone to happen. Epidemiological investigations show that the incidence of esophageal stenosis caused by various diseases is 1.1 per 100,000 people each year. Among them, the incidence of stenosis after endoscopic mucosal dissection for large-area early esophageal cancer is 56–87%, and the postoperative stenosis rate of full-circumference lesions is as high as 100%. For esophageal stenosis, a common esophageal disease, it is often necessary to place stents to maintain the patency of the esophageal lumen. However, traditional esophageal stents have many problems in clinical applications. In particular, stent displacement occurs from time to time, resulting in the inability to continuously and effectively support the esophagus. The occurrence of restenosis may require the patient to receive treatment again. 4D printing technology provides an innovative solution for optimizing the design of esophageal stents:

4.1.1. Shape memory scaffold

Researchers used shape memory polymers such as TPU/PCL blends to print esophageal stents. These stents have unique shape memory properties. Under body temperature conditions, they can adapt to the shape of the esophagus and closely adhere to the esophageal wall, reducing mechanical damage caused by the mismatch between the stent and the esophageal wall. Relevant studies have shown that after 8 weeks of degradation experiments in vitro, the mechanical properties of the TPU/PCL scaffold remained stable. Meanwhile, cell activity detection was conducted on it, and the results indicated that the cell activity could reach 72.9%, fully demonstrating that this scaffold has good biocompatibility [9, 10].

4.1.2. Dynamic support structure

4D printing technology can design esophageal stents with gradient mechanical properties. During the patient's swallowing process, it dynamically adjusts its own supporting force according to the different pressures borne by the esophagus. When the esophagus is in a static state, the stent can provide moderate supporting force to maintain the patency of the lumen. When the swallowing action occurs, the stent will adjust the supporting force to reduce the discomfort of the patient during the swallowing process [11].

4.2. Repair of esophagotracheal fistula

Esophagotracheal fistula is a relatively serious esophageal disease. The key to treatment is to precisely close the fistula and promote the regeneration of the tissues around the fistula at the same time. 4D printing technology has demonstrated unique application value in the repair of esophagotracheal fistulas.

4.2.1. Biodegradable scaffold

The team led by Li from the Second Affiliated Hospital of Xi 'an Jiaotong University has carried out an innovative research. They used 3D printing technology to fabricate biodegradable extratracheal stents and combined them with thoracoscopic surgery, successfully treating complex pediatric tracheoesophageal fistulas. After being implanted in the body, this biodegradable stent can gradually degrade over time, avoiding the pain of patients having to undergo a second operation to remove the stent [12]. 4D bioprinting technology provides another new idea for the treatment of esophagotracheal fistula, that is, combining the patient's autologous cells with the stent to construct a cell-loaded stent. After being implanted into the body, the autologous cells can grow and proliferate on the stent and secrete extracellular matrix to promote the regeneration of the tissues around the fistula, ultimately achieving fistula repair [13].

4.3. Intelligent treatment of radiation esophagitis

Because the squamous epithelium of the esophagus is relatively sensitive to radioactive substances, radiation esophagitis is highly likely to be induced during local radiotherapy for tumors such as esophageal cancer and lung cancer. Its typical symptoms include dysphagia, pain behind the sternum, a burning sensation, etc. Some patients may also develop serious complications such as esophageal perforation or esophagotracheal fistula. A research team from Pohang University of Science and Technology in South Korea has developed a 3D-printed scaffold based on extracellular matrix (dECM) hydrogel. After loading anti-inflammatory drugs, this scaffold can continuously release the drugs to the inflammatory site in a sustained-release manner, which can alleviate the inflammatory response in rat models [14]. 4D printing technology is expected to further optimize such stents on this basis. For instance, by using pH-responsive hydrogels as stent materials, the stents can target and release drugs under the stimulation of the acidic microenvironment in the area of radiation esophagitis, thereby enhancing the precision of drug treatment [15].

4.4. Construction of tissue-engineered esophagus

4D bioprinting technology provides brand-new concepts and methods for the construction of tissue-engineered esophagus.

4.4.1. Dynamic bracket design

Using materials with good biocompatibility, such as collagen and gelatin, esophageal scaffolds with pore gradient structures were fabricated based on 4D printing technology. These scaffolds can provide physical support for cell adhesion and growth. The pore gradient structure within them can also simulate the mechanical environment during esophageal peristalsis, accelerating the orderly growth and differentiation of cells on the scaffolds. A tissue-engineered esophagus with functions closer to those of a natural esophagus is also constructed [16].

4.4.2. Vascularization technique

Vascularization is a key challenge in the process of constructing tissue-engineered organs, and this is no exception even for the esophagus. The scaffold structure was rationally designed by using 4D printing technology to induce angiogenesis. For instance, specific microchannel structures were constructed inside the scaffold to guide the growth of vascular endothelial cells, and blood vessels were formed within the scaffold, effectively solving the blood supply problem of tissue-engineered esophagus [17].

5. Challenges and future prospects

5.1. Technical challenges

At present, when the existing intelligent materials are applied in the treatment of esophageal diseases, there are many areas that need improvement. Although the biocompatibility of this material can meet the requirements to a certain extent, there is still room for improvement. In terms of mechanical properties, continuous optimization is also necessary to better adapt to the pressure changes of the esophagus during swallowing, as well as the stretching and compression during esophageal peristalsis. The issue of degradation rate also needs to be paid attention to, so that the material can degrade at the expected rate and be absorbed or excreted by the human body after completing its therapeutic mission, avoiding poor therapeutic effects due to rapid degradation or adverse effects caused by residual degradation due to slow degradation [18].

The esophagus is a complex and delicate organ. To achieve the wide application of 4D printing technology in the treatment of esophageal diseases, it is necessary to break through the technical bottleneck of multi-material and high-resolution printing. During the printing process, it is necessary to precisely control the distribution and proportion of various materials to meet the performance requirements of different parts of the structure, such as the bracket [19].

5.2. Clinical transformation challenges

Medical devices manufactured by 4D printing technology have the characteristic of customization, which brings challenges to the traditional medical device approval process. At present, the approval standards and procedures for customized medical devices are still not perfect and need to be further standardized. Bioprinting also involves the use of biological materials, such as the patient's own cells, and ethical issues, such as the legality of cell sources and the protection of patient privacy, also need to be urgently addressed [20].

The equipment cost of 4D printing technology itself is relatively high. Moreover, personalized treatment requires customized design and printing based on the specific conditions of each patient, which further increases the treatment cost. This high cost may limit its wide application in clinical practice and make it difficult to benefit more patients. Therefore, how to reduce costs and improve the cost-effectiveness of 4D printing technology in the treatment of esophageal diseases is one of the key issues for achieving its clinical popularization.

5.3. Future directions

The further development of 4D printing technology in the treatment of esophageal diseases requires in-depth collaboration among multiple disciplines, such as materials science, biology, and clinical medicine. Materials scientists are committed to developing smarter materials with better performance to meet the needs of esophageal disease treatment. Biologists need to conduct in-depth research on the interaction mechanism between cells and materials, while clinicians should propose targeted treatment plans and improvement suggestions based on actual clinical needs, jointly promoting technological breakthroughs in the treatment of esophageal diseases with 4D printing technology.

The introduction of artificial intelligence (AI) technology is one of the important directions for the future development of 4D printing technology. AI can analyze a large amount of clinical data and patient information, and accordingly optimize the design of medical devices such as stents to make them more in line with the individual needs of patients. AI can also assist in optimizing printing strategies, continuously improving printing efficiency and accuracy, and promoting the development of 4D printing technology in the treatment of esophageal diseases.

6. Conclusion

In conclusion, 4D printing technology, as an emerging technique, has demonstrated great potential in the treatment of esophageal diseases. It offers brand-new ideas and methods for the treatment of esophageal stenosis, esophagotracheal fistula, radiation esophagitis, and other diseases. In the future, it is also expected to achieve personalized and dynamic precise treatment. Despite this, the research on 4D printing technology in the treatment of esophageal diseases is still in its early stage at present. It faces various challenges both in terms of technology and clinical transformation. In the future, it is necessary to continuously innovate technologies and materials, improve printing accuracy, strengthen clinical verification, solve regulatory and ethical issues, and reduce costs. This gives more options to patients with esophageal diseases.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Munafo R, Saitta S, Tondi D, et al., 2025, Automatic 4D Mitral Valve Segmentation from Transesophageal Echocardiography: A Semi-Supervised Learning Approach. Medical and Biological Engineering & Computing, 2025: 1–16.

[2] Fioretti G, Tolomei A, Ciaramella P, et al., 2024, Study of Degenerative Mitral Regurgitation Using Three-Dimensional Echocardiography and EchoPAC GE Health Care Software 4D Auto MVQ: Comparison Between Transthoracic and Transesophageal Examination. Echocardiography, 41(12): e70040.

[3] Papadopoulos K, Ikonomidis I, Coisne A, et al., 2024, Initial Experience with the 4D Mini-TEE Probe in the Adult Population. Journal of Clinical Medicine, 13(21): 6450.

[4] Goudie E, Kou W, Pandolfino EJ, et al., 2024, Four-Dimensional Impedance Manometry in Esophageal Motility Disorders. The American Journal of Gastroenterology, 120(5): 1019–1026.

[5] Karam R, Elged AB, Elmetwally O, et al., 2024, Porto-Mesenteric Four-Dimensional Flow MRI: A Novel Non-Invasive Technique for Assessment of Gastro-Oesophageal Varices. Insights into Imaging, 15(1): 231.

[6] Sanchis L, Guillen CP, Flores E, et al., 2024, A Minimalist Approach for Left Atrial Appendage Occlusion with the Use of a Mini-Transesophageal 4D Probe. Revista Espanola de Cardiologia, 78(2): 156–158.

[7] Wei G, Wu G, Zeng S, et al., 2025, Biomechanical Properties of 3D Printed Customizable Thermoplastic Polyurethane/Polycaprolactone Hybrid Esophageal Stents. Journal of Composite Materials, 2025(1): 504–513.

[8] Pitisuttithum P, Goudie E, Araujo KI, et al., 2024, Four-Dimensional Impedance Manometry Volume Metrics for Predicting Abnormal Bolus Retention. Neurogastroenterology and Motility, 36(7): e14803.

[9] Ji J, Xiang Y, Dong J, et al., 2024, Four-Dimensional Flow Magnetic Resonance Imaging for Noninvasive Diagnosis of Clinically Significant Portal Hypertension and High-Risk Gastroesophageal Varices in Patients with Cirrhosis. EngMedicine, 1(1): 100001.

[10] Zhang J, Xie Y, Yu S, et al., 2023, Research on the Accuracy of 3D Printed Model of Left Atrial Appendage Based on Three-Dimensional Transesophageal Echocardiography Data. Clinical Ultrasound Medical Journal, 25(11): 875–879.

[11] Javier UU, Vicente VDM, Sergio JH, et al., 2023, 4D-Flow Cardiovascular Magnetic Resonance Versus 3D

Transesophageal Echocardiography in Multifenestrated Atrial Septal Defect. Circulation. Cardiovascular Imaging, 16(12): e015776.

[12] Yu P, Wei G, Huang S, et al., 2023, Biomechanical Properties of 3D Printed TPU/PCL Blend Esophageal Stents in the Esophagus. Engineering Plastics Applications, 51(9): 123–129.

[13] Yao W, Wang J, Zhu L, et al., 2023, Epigenetic Regulatory Factor KDM4D Inhibits Tumorigenesis by Regulating the SYVN1/HMGB1 Ubiquitination Axis in Esophageal Squamous Cell Carcinoma, thesis, Zhengzhou University.

[14] Hassan M, Abdrabou MM, Wahba WA, et al., 2023, Agreement Between 4D Transesophageal Echocardiography and Multi-Detector Computed Tomography in Measuring Aortic Root Dimensions and Coronary Ostia Heights. The International Journal of Cardiovascular Imaging, 39(8): 1561–1569.

[15] Lewis G, Nicholas O, Gwynne S, et al., 2023, A Simplified Method for Delineation of Target Volumes in 4D Oesophageal Cancer Radiotherapy. Radiotherapy and Oncology, 182(S1): S1100–S1101.

[16] Mahmoud BD, Schulz-Siegmund M, 2023, Utilizing 4D Printing to Design Smart Gastroretentive, Esophageal, and Intravesical Drug Delivery Systems. Advanced Healthcare Materials, 12(10): 256.

[17] Chen S, Xing X, Hou X, et al., 2023, The Molecular Pathogenesis of Achalasia: A Paired Lower Esophageal Sphincter Muscle and Serum 4D Label-Free Proteomic Study. Gastroenterology Report, 11: 1–10.

[18] Koronaios A, Politis P, Ntaidou T, et al., 2022, Real-Time 4D Transesophageal Echocardiography in the Evaluation of Cardioaortic Embolism: The Value of Completing a Comprehensive Protocol. Intensive Care Medicine, 49(3): 351–352.

[19] Kou W, Carlson DA, Kahrilas PJ, et al., 2022, Normative Values of Intra-Bolus Pressure and Esophageal Compliance Based on 4D High-Resolution Impedance Manometry. Neurogastroenterology and Motility, 34(10): e14423.

[20] Feng H, Shan J, Ashman JB, et al., 2021, Technical Note: 4D Robust Optimization in Small Spot Intensity-Modulated Proton Therapy (IMPT) for Distal Esophageal Carcinoma. Medical Physics, 48(8): 4636–4647.