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Review Article

3D Printing in Urology, The Current Position, And the Future: Review Article

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Abstract

Objectives: To review the literature of 3D printing or additive manufacturing and its use to create patient-specific replicas to help patients, surgeons, and trainees.

Materials and Methods: We searched the databases of PubMed and Hinari for reports in English, using the keywords "Printing, Three-Dimensional", "3D Printing", "Three-Dimensional Printing", "3DP", and "urinary tract".

Results: We identified 50 articles from the databases. Data was manually extracted from the 50 studies. We searched the criteria for studies that addressed the clinical application of 3D printing in Urology.

Conclusions: The main applications are in training and planning surgical procedures, kidney replacement and transplantation, drug testing, therapeutics, toxicity, and cancer therapy, and patients' understanding and education.

Keywords: 3D Printing; 3DP; Urinary Tract; Printing; Three-Dimensional

Abbreviations

PCS	:	Pelvicalyceal System
PCNL	:	Percutaneous Nephrolithotomy
CT	:	Computerized Tomography
MRI	:	Magnetic Resonance Imaging
PN	:	Partial Nephrectomy

Introduction

Charles W. Hull first described 3D printing in 1986. He named it 'stereolithography'. Layers of a material that were treated with ultraviolet light were printed in sheets to form a solid 3D structure. This is transplanted after *in vitro* maturation [1]. 3D prints can demonstrate nephrotoxicity of medicines and its prevention [2]. Platforms can imitate *in vivo* conditions and tubular microenvironment [3]. Three-dimensional printing creates a kidney graft and pelvic cavity imitating the living kidney. This helps surgeons and residents to treat the given condition before surgery. It reduces operation time of kidney transplantation surgery [4]. 3D printing or additive manufacturing is used to create patient-specific models to help surgeons and trainees. Furthermore, it helps in further aspects including dose verification in radiation therapy and in forensic issues. 3D printing is efficient and cheaper than other tools [5]. Organ preservation would improve, thereby helping to relieve the organ shortage through increased availability and quality of donor organs [6]. 3D printed pelvicalyceal system was used before percutaneous nephrolithotripsy as Plasticine 3D models of pelvicalyceal systems were made. CT software, magnetic resonance images and ultra sound provides reconstructed 3D images of the PCS and used for PCNL [7]. This is a narrative review of the existing literature. In addition, we will summarize the present available uses of 3D printing and the potentials of future applications.

Materials and Methods

Sources

The review comprised a literature search of PubMed and

Hinari for reports in English, using the keywords "Printing, Three-Dimensional", "3D Printing", "Three-Dimensional Printing", "3DP", and "urinary tract". This review includes the 50 articles identified. All articles published up to June 2017 were included.

Data Abstraction

Our literature searches yielded printing techniques to model native biology with preservation of cellular function. Issues as dose verification in radiation therapy and in forensic topics were looked for, in addition to other matters as nephrotoxicity and creating kidney grafts imitating the living kidney.

Results

Our search identified 50 articles that were included in the final review. Study results were afterward entered into a table (Table 1).

Ref.	Application
1 [1]	3D-bioprinted tissues are used in transplantation, drug discovery, analysis of chemical, biological and toxicological agents, and research.
2 [2]	3D is an ideal means to study nephrotoxicity
3 [3]	Kidney-on-a-chip may be able to establish structures that can replace function.
4 [4]	Models were used to plan and guide laparoscopic donor nephrectomy and recipient transplantation
5 [5]	development of quality assurance (QA) program ensured the required accuracy
6 [6]	models for organ preservation could relieve the organ shortage crisis
7 [7]	3D printing technology helps in patients' understanding of their disease and the surgical procedure.
8 [8]	Surgery was preceded by an operation carried out in a silicone model of laparoscopic simulator in which the tumor was excised. Tumor was excised. Period of ischemia was few minutes.
9 [9]	Pre-operative physical 3D models created from MRI data may influence surgical planning for complex kidney cancer.
10 [10]	In-exendin has a high uptake in the kidneys versus low uptake in the pancreas.
11 [11]	In urology, 3D printing of models was used for the pre-surgical planning of partial adrenalectomy, partial nephrectomy and for educating patients
12 [12]	More exploration of nanomaterials-based bioinks is needed.
13 [13]	3D printing applications is used to regenerate organs and tissues
14 [14]	Applications for 3D printing include tissue and organ fabrication; prosthetics, implants, anatomical models, and drug dose
15 [15]	Structure created can lead to the function desired.
16 [16]	3D models help trainees to develop their surgical skills.
17 [17]	Having a printer in a central and open location like a library can help scientists, doctors, and students.
18 [18]	The use of 3D bio-printed models is used in oncology research in clinical cancer therapeutics.
19 [19]	After training on 3D model, PCNL proceeded without complication.
20 [20]	3D printed models assisted in the first adult-to child kidney transplant.
21 [21]	Bioprinting has the advantage of good resolution of the input cells during attempts to print kidneys and other organs.
22 [22]	Drug-testing is one of the targets. Animal models could be partially replaced by biofabricated tissues.
23 [23]	it was possible to perform a low-cost mock kidney fine needle aspiration (FNA) procedure
24 [24]	(bio-ink) enabled to create implantable devices such as bio-degradable tissue engineering scaffolds.
25 [25]	The ability of 3D printing to produce organ transplants will overcome finding kidney donors.
26 [26]	Decellularization of cadaveric organs was followed by repopulation. Later 3D bioprinting was used to deposit cell-laden bio-inks to attain complex tissue architecture. As a future aim, heart, kidney, and liver creation may be possible.
27 [27]	3D printing reduces the need for organ donors. It eliminates problems arising from immunosuppression as it uses the patient's own cells
28 [28]	CT reconstruction, ultrasound examination, and endoscopy showed that the designed phantom mimics a real kidney's detailed anatomy.
29 [29]	3-D printers make cost-effective custom-made structures for use.
30 [30]	Organ printing enables biofabrication of human organ constructs with a 'built in' intra-organ branched vascular tree.
31 [31]	3D models of kidney are needed for drug screening and kidney organ engineering

32 [32]	3D printed models are useful in planning PCNL access, are relatively of low cost, and reproduce the anatomy of the renal collecting system.
33 [33]	Bioprinted 3D proximal tubule model can serve as a test bed for the assessment of human nephrotoxicity
34 [34]	3D silicone mold (cavity) can be used in surgical training programs.
35 [35]	In medical 3D printing literature, terminology is used to obtain synonymous definitions.
36 [36]	Balancing safety and efficacy with the autonomy of individuals in the field to make the greatest positive impact on healthcare
37 [37]	Personalized medicine is now delivered by "clinical modelers",
38 [38]	Complex tissue structure fabrication is an efficient tool for drug discovery and preclinical testing.
39 [39]	Operations were successfully completed without clamping. During PN, the surgeons confirmed the accuracy of the reconstructed 3D images and surgical simulations in all cases. Patients answered that the 3D images had helped them understand.
40 [40]	Average times of image segmentation, casting mold design, casting mold printing and pouring of silicon replicas were 94 min, 22 min, 14 h and 30 min, Average costs of casting mold printing and casting of silicon replica were 14.4$ and 7.4$ respectively.
41 [41]	Models of renal units with malignancies before surgery were constructed. Patients and trainees stated that the models enhanced understanding of the surgery.
42 [42]	Models of T1N0M0 tumors with 3D printing were presented to urologists for training. Understandings from patients were well appreciated.
43 [43]	3D printed phantoms can be functionally equivalent to commercially available phantoms.
44 [44]	Progress made so far is promising creating the complex vascular system needed to keep the tissues alive
45 [45]	Printing human cells produced blood vessels and beating heart tissue. 3D tissue structures could be used to test pharmaceutical
46 [46]	Through CT and MRI scans, the 3D printer produced a model that enabled surgeons to assess the feasibility of the transplant and to rehearse steps of the operation.
47 [47]	Partial nephrectomy was in 90 minutes. This would have taken hours if it were without the 3D printed models, blood loss was 50 ml.
48 [48]	Viewing their personal 3D kidney model, patients demonstrated an improvement in understanding of basic kidney physiology & anatomy.
49 [49]	A method was developed to be used in surgical simulation and training.
50 [50]	Organ models were created for the utility of tissue-engineering

All articles were in English. Of these articles, 10 were concerned with training and planning surgical procedures. Along with our selected articles, they were concerned with transplant surgery, tumor nephrectomy, PCNL training and needle (biopsy, and aspiration). With kidney (replacement and transplantation), there were 11 articles. Three-dimensional (3D) external geometry was used in tissue engineering and 3D printing. Plastic, metal, ceramics, powders, liquids, or even living cells are used in layers. Bio-ink to create implantable devices was developed. The final aim is to overcome finding kidney donors and to abolish immunosuppression problems. On the subjects of drug testing, therapeutics, toxicity, and cancer therapy, we included 10 articles. Printing applications include organ fabrication; creation of customized prosthetics, implants, anatomical models, and drug dosage. Models that review human responses are needed for drug screening. A 3D printer can build tissue structures for the use in testing pharmaceuticals. In the case of patients' understanding and education, we included 5 articles. Tailored 3D models of pelvicalyceal systems were shown to patients before percutaneous nephrolithotripsy, partial adrenalectomy, and partial nephrectomy. It helped them understand their disease.

Training and Planning Surgical Procedures

Three D models where obtained from MRI data [9]. Models as well were based on abdominal CT images, they were used in patients scheduled to undergo PCNL. Wax printing judged by CT reconstruction showed that the phantom imitates kidney's anatomy [28]. This allowed staff and residents to train and later the operations were performed, and patients could be discharged after one day [19]. Models were used to plan surgical procedures for laparoscopic donor nephrectomy and recipient transplantation surgery [4]. In tumors, the operation was first carried out in a silicone model then laparoscopic removal of the tumor was performed with reduced ischemic time to only few minutes [8]. Applications for pre-surgical planning of partial adrenalectomy, partial nephrectomy in renal tumors, and for educating patients were used [11]. These models help learners to develop their skills [16]. Adult-to child kidney transplant became easier [20]. World first 3D printing used in kidney transplant was performed in 2016.

A kidney was donated by a child's father, then models of father's kidney and child's abdomen were produced using Guy's and St Thomas' 3D printer. Surgeons could plan the operations to reduce the risks [46]. Fine needle aspirations could also be taught ahead of the procedure [23].

Kidney Replacement and Transplantation

3D-bioprinted tissues are used in transplantation, printing tissues, hollow tubes such as blood vessels, and solid organs such as the kidney [1]. Nano 3D printing has advantages over micro fabrication. Research is concentrating on 3D printed kidney-on-a-chip platforms [3]. Structured-light scanning techniques could shift the model for organ preservation. This relieves the organ shortage crisis by increased availability and quality of donor organs [6]. With the three-dimensional (3D) external geometry was used in tissue engineering and 3D printing, it is possible to regenerate organs and tissues with modified geometries to treat defects or injuries [13]. Materials such as plastic, metal, ceramics, powders, liquids, or even living cells are used in layers to produce a 3D object that is used in tissue and organ fabrication [14]. Artificial tissues and organs are printed by depositing cells, biomaterials, and molecules layer by layer. Attempts are made to print kidneys and other organs [21]. The development of (bio-ink) is one of the goals of 3D printing. It has enabled to create implantable devices such as biodegradable tissue engineering scaffolds [24]. 3D printing produces organ transplants that may overcome finding kidney donors. Furthermore, it would abolish immunosuppression problems and transplant rejection because it uses the patient's own cells [27]. Organ printing allows fabrication of human organs with a 'built in' intra-organ branched vascular tree [30]. 3D human renal proximal tubules were created *in vitro*, they are embedded in an extracellular matrix and are perfusable. The epithelial morphology and functional properties are the same as the control. Bioprinting methods provide human kidney tissue models on demand [31]. Furthermore, 3D printing of plastic or collagen allows constructing scaffolds on which cells can grow [45].

Drug Testing, Therapeutics, Toxicity, and Cancer Therapy

Tissues are printed for best possible protection of cellular function and transporter activity. This provides a perfect way to study nephrotoxicity [2]. Applications printing include organ fabrication; creation of customized prosthetics, implants, anatomical models, and drug dosage [14]. Models could simulate the microenvironment. Bio-printing of live human cells is used in oncology research in clinical cancer therapeutics [18]. Stem cells that are used as a controlled environment can be produced to affect cell growth and differentiation. Animal models could be partially replaced by biofabricated tissues [22]. Three-dimensional models of kidney tissue that review human responses are needed for drug screening, disease modeling, and, ultimately, kidney organ engineering [31]. Bioprinted 3D proximal tubule model can serve as a test of nephrotoxicity aided by the development of pathogenic states involving epithelial-interstitial interactions [33]. Investigators who model disease with 3D printing to define pathology, plan intervention, and treat patients [37]. Bioprinting is used in tissue structure fabrication based on the medical images, and is an efficient tool for drug discovery and preclinical testing [38]. Creating the complex vascular system to keep the tissue alive will help in therapeutic applications [44]. Printers has been developed to build 3D tissue structures that could be used to test pharmaceuticals [45].

Patients' Understanding and Education

Personalized Plasticine 3D models of pelvicalyceal systems were shown to patients before percutaneous nephrolithotripsy. It helped in their understanding of the disease and the surgical process [7]. Anatomic models were used for the planning of partial adrenalectomy, partial nephrectomy in the resection of renal tumors, and for educating patients [11]. Patients with renal cell carcinoma underwent clampless PN (partial nephrectomy). All patients answered that the 3D images had helped them understand their disease status and surgical risks [39]. Models of patients' kidneys before surgery were made. Those patients had partial nephrectomy for their renal tumors and had the advantage of short ischemia time. Patients and trainees asserted that the models improved their understanding [41]. After inspecting their own 3D kidney model, patients had improved understanding of kidney physiology and anatomy [48].

Discussion

3D printing in medicine has been rising dramatically and quickly [50]. Objects that have been printed in this field show the capability of this know-how in healthcare prospects. So far, twelve Items have been printed; they are:

- Tissues with blood vessels
- Prosthetic Parts
- Drugs
- Heart attached sensors to detect oxygenation
- CT and MRI models to orientate doctors
- Bone
- Heart Valve
- Ear cartilage
- Medical equipment
- Cranium Replacement

- Synthetic skin
- Organs

Training and surgical planning is one of the main successes of 3D printing. Structured-light scanning techniques enabled the 3D topographical matching of microfluidic device geometry to porcine kidney anatomy [6]. Materials used include acrylonitrile butadiene styrene (ABS) that has impact resistance, toughness, high radiodensity, and low cost. Printers use a polymer filament (that is heated to a liquid state in a printer head) and deposited in predefined locations corresponding to the model shape [7]. 3D printed models are useful in planning PCNL access. They provide a model for training in PCNL access [32]. Furthermore, it is used in the presurgical set up for laparoscopic and robotic partial nephrectomy [34] in renal cell carcinoma. Kidney models of T1N0M0 tumors were shown to urologists for planning and training. Operations were completed without clamping, with negative surgical margins and minimum or no blood transfusions. The surgeons confirmed the accuracy of the reconstructed 3D images and surgical simulations in all cases. In patients undergoing laparoscopic kidney tumorectomy due to renal cell cancer, average time of preparation is about 16 hours and 30 minutes. The average costs of casting mold, printing and casting of silicon replica were about 22 $ [40]. Renal tumor excision after practicing on a 3D replica can take only 90 minutes. It would have taken much longer time [47].

In kidney replacement and transplantation issue, the failure of organs and tissues is a difficult problem. 3D bioprinting was started by Dr. Anthony Attala from Wake Forest Institute for Regenerative Medicine, who applied 3DP to manufacture organ tissues of heart and kidney. Chinese investigators reported the 3D bioprinting of tissues of kidney replacement. Organovo is a company in the 3D bioprinting field. They have printed liver and kidney tissues [20]. The inadequate supply of organs has induced research on the design of a cell-scaffold microenvironment to help the regeneration of various types of tissues. Bioprinting is used in tissue engineering for the fabrication of scaffolds, cells, tissues, and organs. It is divided into three groups, inkjet-based bioprinting, pressure-assisted bioprinting and laser-assisted bioprinting. Bioprinting uses biomaterials, cells, or cell factors as a "bioink" to make tissue structures [21]. Artificial tissues and organs are printed by depositing cells, biomaterials, and molecules layer by layer. Bioprinting has good resolution of the input cells. Kidneys and blood vessels are on the list [21] World first 3D printing was used in kidney transplant in 2016. Surgeons at Guy's and St Thomas' have lead the way to the world's first use of 3D printing to help in a successful transplantation of an adult kidney into a two-year-old child using a kidney donated by her father. Models of donor and recipient abdomen based on measurements obtained through CT and MRI scans were produced using Guy's and St Thomas' 3D printer so that the surgeons could accurately plan the operation to minimize the risks. It is the first time in the world that 3D printing has been used to help kidney transplant surgery involving an adult donor and a child recipient [46].

As for drug testing, therapeutics, toxicity, and cancer therapy; The cellular and architectural structure of ExVive™ Human Kidney Tissue provides an ideal means to study the many phenotypes of nephrotoxicity including tubular transport. An example is Cisplatin-mediated nephrotoxicity and its prevention by cimetidine. This was well shown in ExVive™ Human Kidney Tissue [2]. 3D printing is being used in drugs development. This is achieved by 3D printing by personalized medications. Pharmacists could analyze a patient's profile, such as age, race, or gender, to determine an optimal dose. They could then print and dispense the personalized medication via an automated 3D printing system. Patients who have multiple diseases could have their medications printed in one multi-dose form providing patients with an accurate single dose. Bone infections are another example where direct treatment with a drug implant is more desirable than systemic treatment [14]. 3D bio-printed tissues and organs are used in the preclinical testing and therapeutics of anticancer drugs [18]. 3D biofabrication will help in drug testing where animal testing may be replaced by use of 3D biofabricated tissue. Drugs-by either themselves or embedded in microspheres or nanospheres-could be deposited within the construct optimizing the tissue formation. Furthermore, it is possible to transfer genes into cells by inkjet printing in addition to the precise delivery of the modified cells to a given target [22]. In drug toxicity testing, Cyclosporine A, a drug given to prevent rejection, is a known nephrotoxin that damages proximal tubule cells. To study its effect a perfused 3D proximal tubule model, was exposed to various concentrations of Cyclosporine A (CysA) then alterations of cell morphology were monitored [31, 33].

Concerning Patients' understanding, and education 3D information helps patients in choosing treatments [7]. Models have been used for educating patients about the anatomy of their kidney and tumor before resection [11]. Urosurgeons asked patients whether the 3D images had helped them understand their operations more clearly than 2D images would have. All patients answered that the 3D images had helped them understand their disease status and surgical risks [39]. Patients and trainees could use the individualized model before certain operations as partial nephrectomy [41]. Patient nicely understood the disease and procedure.

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