Abstract:

Three-dimensional (3D) printing was invented in 1983 but has only just begun to influence the fields of medicine and surgery. The conversion of digital images into physical models demonstrates promise to revolutionize multiple domains of surgery. In the field of urology, researchers and clinicians have recognized the potential of this technology and are working towards making it an integral part of urological practice. We sought to review current literature regarding 3D printing and 3D technology in the field of urology.

Method

A systematic review of the literature was performed according to a modified PRISMA analysis. Medical databases that were searched include: Web of Science, EMBASE and Cochrane databases. Articles assessed were limited only to English-language peer-reviewed articles published between 1980 and 2017. The search terms used were "3D", "3-dimensional", "printing", "printing technology", "urology", "surgery". Acceptable articles were reviewed and incorporated for their merit and relevance with preference given for articles with high impact, original research and recent advances.

Results

A small number of studies exist utilizing this emerging technology in its educational, clinical and prosthetic domains. These show promising results but further research is required and cost reduction must occur before clinicians fully embrace its use.
Conclusions
As costs continue to decline and diversity of materials continues to expand, research and clinical utilization will increase. Recent advances have demonstrated the potential of this technology in the realms of education and surgical optimization. The generation of personalized organs using 3D printing scaffolding remains the 'holy grail' of this technology.
Dear Sirs,

Thank-you for your invitation and consideration of our manuscript “Three Dimensional Models in Urology: A future built with additive fabrication” for publication in The World Journal of Urology. We reviewed contemporary literature to provide a summary of the advancements in 3D printing and 3D reconstruction in the field of Urology. These findings are of interest to your readership.

The authors confirm that there are no conflicts of interest and this manuscript has not been submitted to an alternate journal.

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Three Dimensional Models in Urology: A Future Built with Additive Fabrication

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Introduction

Since its invention by Chuck Hull in 1983, three-dimensional (3D) printing has transformed the fields of engineering and manufacturing and has already begun to revolutionize several domains in health care. The conversion of digital images into physical models has delivered a broad range of medical and surgical applications including tissue fabrication, customized prostheses, patient education, anatomical models and pharmaceutical development[1].

As imaging modalities, biomaterials and printing processes increase in their sophistication, integration into various arenas of medicine will become progressively dominant. Urological practice will develop greater personalisation and democratisation of patient care. 3D printing technology has the potential to change the way in which clinicians educate, learn and operate by vastly expanding the tools at the disposal of the Urologist

What is Three-Dimensional Printing?

Traditional manufacturing often employs a subtractive process to progressively remove material by drilling, cutting and sanding an object from a mold. Conversely 3D printing is an additive fabrication process used to make a three-dimensional entity reconstructed from a series of two-dimensional (2D) images. This reconstruction can be created from multiple imaging modalities including high-resolution ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). Importantly, specialised modelling software is used to collate multiple 2D images to construct a digital 3D object which is then transcribed into a physical product by stacking successive layers of material using a 3D printer[2]. Figure 1 displays a flowchart regarding a standard 3D printing workflow.

Technologies for layering materials most commonly utilise fused deposition modelling (FDM), but can also achieve this with selective laser sintering (SLS) and stereolithography (SLA). These various techniques have incorporated materials such as ceramic, silicon, titanium and live cells to the ever-increasing portfolio of viable printing materials[3,4]. This has allowed 3D printing to evolve from the prototype stage into feasible technology suited to personalised medicine in multiple specialties. The ability to utilise different materials allows for the accurate modelling of behaviour and destruction of tissues and opens the door for a wide range of applications including simulated operative training on lifelike prostheses. As the portfolio of 3D printed materials continues to become more sophisticated and increase in accessibility, its influence on the fields of medicine and surgery will continue to expand.

Accessibility and Type of Modelling

One of the factors limiting the dissemination of 3D printing technology are the involved costs. The rapid pace of advancement has resulted in a high degree of variability in this area. The most cost-effective technique to date is FDM as it allows for rapid, patient-specific hard plastic anatomical models to be printed. Although relatively inexpensive, restrictions regarding component material (plastics) limit its use to modelling for educational purposes and tactile components of the modeling are limited. The ink for the printers involved cost approximately $30 (USD) per kilogram roll[5].

SLS is costlier and involves sintering powders such as metals, plastics and ceramics which are added layer by layer. These machines can cost upwards of $100,000 (USD) to install. However, they have the ability to manufacture patient-specific metal prostheses[5].

SLA utilises an ultraviolet laser directed via dynamic mirrors to scan over a vat of ultraviolet curable photopolymer, solidifying specified parts on the surface of the liquid. Formation of the 3D printed model occurs when new layers of photopolymer are cured upon the layer below. SLA and PolyJet generate high resolution models which can mimic the tactile properties of human tissue. These properties make this printing technology desirable in anatomical modelling and surgical simulation. The cost of these
technologies can be highly variable based on the cost of equipment and resin, with some groups spending approximately $500 (USD) per model[6].

3D printing and Surgery

Literature regarding 3D printing in the critical care[7] and surgical field is growing exponentially with clear opportunities for further studies to be conducted across many medical disciplines. 3D printing technology has been used in a vast array of surgical domains to date. Initially adopted for use in the field of education, it has also been applied in preoperatively planning and empowering patients with greater understanding of their condition and the complexities of spatial components of anatomy. In orthopedics 3D printers have been utilised for customizable implants in difficult cases (i.e. revision arthroplasty)[8] as well as novel use in customizable casts that are more lightweight and water proof than traditional plaster casts. Maxillofacial surgeons have also begun to see benefit in 3D printed technology with use in 3D printed jaw prostheses[9]. This uptake has also been displayed within the field of Urology with the early adoption of 3D printing predominantly used in the education of patients and surgical approaches to renal masses.

To highlight the advancements, ease, timeliness, usefulness and clarity of 3D printing technology for this review, our team created our own 3D model. We utilised axial CT images of a patient with known renal cell carcinoma to reconstruct the patient’s left kidney. We went on to print a model using a clear resin to represent the renal parenchyma and blue resin to represent the in-situ tumor. Additional color-coding was used to highlight the renal vasculature (renal artery in pink and renal vein in purple). The finished product of the model is displayed in Figure 2. From image data importation to the finished model, the process took just under a week.

3D Printing in Urology

Education

Patient and trainee education is a challenging task for Urologists. Relaying complex oncological and anatomical information using 2-dimensional computer images is an ongoing responsibility that can be facilitated with the use of 3D printed organs. Silberstein and colleagues demonstrated the use of 3D printed renal models as tools in the education of patients and surgical trainees, resulting in enhanced comprehension of the anatomy and intended surgical intervention prior to undergoing robotic partial nephrectomy. 3D models were particularly useful for surgical residents, who benefitted from the ability to reference anatomical landmarks intraoperatively[10].

The utility of 3D printing for patient education was underscored by a follow up study lead by Bernhard et al. This team demonstrated that 3D printed renal models elicited superior standardized survey scores when assessing patient understanding of kidney physiology, anatomy, tumor characteristics and planned surgical intervention when compared to traditional education using CT images. With improved understanding of their disease and surgical intervention, patients reported a higher overall satisfaction in their surgical experience[11].

In addition to use within the hospital environment, many universities are now fully incorporating 3D printing and reconstructive technologies such as Virtual Reality (VR) into their departments of anatomy. Contemporary medical students and graduates now have experience in the creation and utilization of models in conjunction with standard wet-lab specimens throughout their undergraduate or post-graduate education. The use of these 3D models in this environment has obvious advantages in highlighting particular characteristics of anatomy as well as reducing the costly need for human cadaveric donations[12].
Surgical Planning

The ability for 3D printing technology to depict detailed soft tissue and vascular anatomy has given rise to its utility in preoperative planning for urological procedures. The most detailed studies to date have examined the role of 3D printing in pre-surgical simulation prior to nephron sparing surgery. Ukimura et al utilised the 3D reconstructed images used to print physical models in pre-operative assessment of patients undergoing robotic assisted laparoscopic partial nephrectomy (RALPN). In this small case series, the images facilitated micro-dissection of the renal vasculature and allowed for successful zero-ischemia RALPN to be performed[13]. A similar approach using 3D reconstructed images only was adopted by Chen et al during the pre-operative planning of laparoscopic partial nephrectomy[14]. In this study, their group took the 3D image platform one step further by superimposing 3D reconstructed images onto 2D laparoscopic images to identify the location of target pathology. Results for the 15 patient series were promising and displayed benefit in surgical outcomes. However, as with most 3D studies, this group lacked a control comparison.

The use of a physical model of the kidney allows the surgeon to manipulate the model and appreciate the tumour size and depth of penetration and can aid in the decision making process to proceed with either radical or partial nephrectomy. Zhang et al printed ten 3D models kidneys with T1 grade renal tumours and presented them to experienced urologists as a tool for preoperative planning. On a follow up survey, all of the surgeons agreed that the models benefited preoperative planning and training[15].

The successful use of 3D printing to accurately model soft tissue urological malignancy has been further applied to aid in preoperative planning of robot prostatectomies. In a recent study lead by Shin et al, translucent whole-gland prostate models were generated for 5 patients using 3D MRI-transrectal ultrasound image-fusion software. 3D printed glands were demonstrated to improve the visualisation of the location, size, and extent of the prostate lesion. For an estimated cost of $500 (USD), surgeons reported enhanced precision and confidence from being able to examine the prostate lesion in detail[6].

These examples demonstrate promise for the use of 3D printing in a small cohort of patients in the pre-operative planning stage. Although larger scale mature data is required before these effects are properly quantified, it is not unreasonable to suggest that the use of 3D models could reduce renal ischemic time or increase application of selective arterial clamping. Furthermore, they could provide the level of confidence needed to change a planned radical surgery to an organ-sparing intervention.

Surgical simulation

With the advent of bio similar resins that more closely resemble living tissue, 3D printing has recently progressed from use in education and pre-operative planning to providing material for surgical simulation. In Urology this has lead to use in areas where knowledge of patient specific complex vasculature and the importance of adequate oncological margins is paramount. One such domain is nephron sparing surgery, namely laparoscopic partial nephrectomy (LPN). It is well established that surgery in this realm can be challenging to perform, especially for complex tumours. Difficulties of the extended learning curve for this operation are increased when performing robotic assisted laparoscopic partial nephrectomy (RALPN) and are precipitated by a paucity of accurate surgical planning and simulation resources. A team lead by Maddox sought to quantify the benefit of pre-operative rehearsal on patient specific 3D kidney models. Each model was constructed from a surgically respectable resin that mimicked the consistency of the target tissues with colour variation to delineate the renal parenchyma, tumour, vascular structures, components of the collecting system and the proximal ureter. Seven models were created for use in simulation of partial nephrectomy and were performed using the da Vinci platform prior to surgery. Outcomes from this pilot reported that patients in which the team performed pre-operative surgical simulation had a lower ischemic time, fewer positive surgical margins, shorter hospitalization, fewer post-operative complications and lower estimated blood loss[16]. Although this was a small proof of principle study with limited statistical power, the results highlight the potential benefits of surgical simulation using 3D printed models for complex renal tumours. These benefits following pre-operative rehearsal of RALPN on biosimilar 3D printed renal models was echoed by a team lead by Rundstedt. This group had a similar approach, performing tumour excision on 10 patient-specific 3D renal models prior to each respective surgery. In this group, however, analysis revealed no statistical difference in operative times between
rehearsal and actual surgery. Comparison of differences between the size of the CT generated image, 3D printed model and excised tumour displayed no statistical difference between groups[17]. Despite the small cohort and low statistical resolution, these results do contribute to a growing body of evidence regarding the efficacy of 3D printed simulations prior to complex surgery.

Surgical simulation on patient specific models allows for factors such as tumour position, depth and proximity of adjacent structures to be encountered and approached in the pre-operative planning stage. Furthermore, 3D reproductions of complex anatomical variations that are difficult to appreciate on traditional 2D imaging, have the ability to revolutionise surgical precision and improve surgical outcomes[18]. Further studies, ideally multi-centre randomised trials, assessing the benefit of pre-operative surgical simulation utilising 3D printed models are required before confidence in their effect can be declared. With early evidence pointing towards gratification of a “practice before you play” model for complicated surgery, addition of surgical rehearsal may eventually add to the standard of care, even for experienced urologists.

The use of 3D in other areas in urology

Relatively recent developments in imaging and surgical device technology at the disposal of Urologists have created a new age of clinical care and parallel expansion of 3D printing technology has lead to its integration in other arenas of urological care. Techniques adopted by radiologists have used Multiplanar Reconstruction (MPR) for several years now in the domains of CT and MRI, culminating in further clarity and detail in diagnostic imaging. Although debate still surrounds the issue of cost effectiveness when creating what some may define as an aesthetic adjunct (versus a clinically useful tool), most accept that the additional spatial information provided by 3D rendering is useful. In the field of Urology this is perhaps most pertinent in surgical decision making and planning for complex cases where triplanar identification of vasculature position of pathology may influence the viability of therapeutic options.

Investigations into intraoperative 3D imaging adjuncts have also shown promise. The benefits of marriage of 3D reconstructions and real-time operative fields have been demonstrated in the laparoscopic [19] and robotic [20] setting of partial nephrectomy. Progressive work is currently being undertaken to incorporate active algorithms and real-time scanning to accommodate for intra-operative tissue destruction, automatically updating imaging models so that surgeons may gain further clarity in the operative field. Some have even incorporated other technologies such as “real time” and “practice” virtual reality[21]. In addition, many have begun to address real-time image guidance and assistance[22]. All of these aspects herald a further step toward robotic integration and automated surgery.

The future of 3D printing in Urology

Apart from previously mentioned uses, many believe the urological future of 3D printing technology resides in the ability to build tissue scaffolds that can then grow replacement organs via bio fabrication. This technique involves the deposition of harvested cells from an individual onto a 3D printed scaffold, eventuating in a new organ that is customised for the recipient. This process removes the need for anti-rejection medications and the physical and psychological difficulties involved in the organ donation process. Although this reality is far from being incorporated into daily practice, labs have shown early promise and success in techniques[23].

Current difficulties of this approach lie in the creation of an organ with multiple physiological functions rather than structural replication alone (ie renal filtration, erythropoietin production and contribution to adjustment of renin and angiotensin in the kidney). To achieve this, multiple cell types and structures need to be created in unison and then grown[24,25].

Other simpler domains, which have yet to be accessed or addressed, seem to lie within the field of reconstructive urology and could include personalised reconstructive penile prosthesis and patient customised sphincters for lower urinary tract reconstructions.
**Barriers remaining in 3D Printing for Medical Applications**

Despite the promise that 3D printing has shown in the medical literature, major barriers exist to the technology being widely adopted that are separate to the obvious financial burden. First of all, Clinicians often lack the technical skills required to segment medical images and print 3D models of their patient’s anatomy. Publications exist which aim to introduce clinicians to digital modelling skills[26,27], but the uptake has thus far been slow.

Secondly, the scarcity of biocompatible materials with which to print patient-specific implantable components limit the use of this approach. Many of these materials are still in the experimental stage of development and are not available to the average clinician[28]. Materials that print in metal or extracellular matrix are still far more expensive than their polymer print counterparts. However, as the patent for SLS metal 3D printers has recently expired we are likely to see a cost-reducing effect, similar to what has occurred with current thermoplastic printers. The cost of these machines are likely to reduce and allow hospitals to obtain the equipment necessary to print their own medical devices in-house.

Thirdly, conventional sterilisation via autoclave requires contact with high temperature (121-132 degrees Celsius) and significant pressure[29], which most 3D printed materials cannot withstand. Other common sterilisation approaches suggested in the literature include ethylene oxide gas, hydrogen peroxide gas, and gamma radiation to sterilise the materials whilst leaving little to no toxic residues. These may provide viable alternatives to this problem, however, they have yet to be explored in detail.

Finally, apart from humanitarian exceptions targeting rare diseases that are able to be approved without proof of effectiveness, regulatory standards have yet to be set regarding the use of personalised 3D printed medical devices and how these should be manufactured. This exposes the potential for exploitation of patients[30,31].

**Conclusion**

3D printing is emerging as a viable technology that may revolutionise the way that we educate patients, plan procedures and guide surgeons through complex cases by providing a detailed, physical representation of patient-specific anatomy. Future developments and cost-reduction could see 3D models, personalised prostheses and orthoses being printed in-house, reducing waiting times involved with third-party products.

The tantalising promise of 3D bio-fabrication of patient-specific artificial organs, ready for implantation, continues to drive researchers and draw interest the medical community. Despite this promise, 3D printing technology has yet to receive full acceptance from the medical and surgical communities. Small studies with limited statistical capacity and short term follow up, as well as the high costs of purchasing image-generating software and printing equipment remain significant hurdles to widespread adoption. These barriers to the emergence of mainstream 3D printing technology will inevitably fall as the diversity of polymers expand to include live tissues and the cost of equipment declines.

The coming years will prove an exciting time as 3D printing continues to democratise the potential of personalised surgery from research institutions to everyday clinical practice. We are truly privileged to live in such dynamic times in the field of Urology.
Authors Contribution Statement

All Authors contributed to the production of this manuscript.

T G Manning: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing
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Conflict of Interest

The authors declare that they have no conflict of interest.

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

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Figure 1: Overview of a Standard 3D Printing Workflow

- Collection of high resolution ultrasound, CT, MRI imaging
- Creation of surface anatomy for organ or tissue using imaging software
- Manipulation of digital models for accuracy and colour-coding anatomical features
- Selection of printing platform and desired resin
Figure 2: 3D Printed Left Kidney using SLC hard resin technology. Displaying renal artery: pink, renal vein: purple and tumour: blue. Anterior view: image A. Posterior view: