R E VIEW PAPER **TRAUMA AND RECONSTRUCTIVE UROLOGY**

Advances in urethral stricture diagnostics and urethral reconstruction beyond traditional imaging: a scoping review

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Introduction Urethral stricture disease is considered one of the more functionally bothersome aspects of urological conditions. The management of such disease is also traditionally managed with urethroplasty, or in severe cases, reconstruction. With the rise of artificial intelligence (AI) playing its part in diagnostics and treatment of urological conditions, we sought to determine its use case in urethral conditions in today's era of advanced surgical care.

Material and methods A comprehensive literature search was performed to identify literature on advances in diagnosis and management of urethral strictures. Publications in English were selected, whilst studies that were case reports, abstracts only, reviews, or conference posters were excluded. **Results** Twelve studies were finalised for review. Conventional neural networks and computational fluid dynamics implemented in retrograde urethrography reduced false positive and negative rates of urethral stricture diagnosis. Four-detector row computed tomography and magnetic resonance imaging voiding with virtual urethroscopy are also emerging imaging combination options for identification, offering decreased duration needed for diagnosis and increased correlation with intraoperative findings of urethral stricturing. For tissue re-engineering for urethral strictures, the role of 3-dimensional bioprinting of both autologous and allogenic sources has been on the rise, with promising findings of sustained tissue viability demonstrated in several *in vitro* animal studies and showing potential for expansion into human utilisation.

Conclusions Advances in detection and management of urethral strictures have steadily been increasing its capacity, especially with the rise in artificial AI-driven learning algorithms and more accurate objectivity. Further studies are awaited to validate the use case of AI models in fields of urethral stricturing disease.

Key Words: radiomics \circ artificial intelligence \circ 3D printing \circ urethral strictures

INTRODUCTION

Urethral stricture disease (USD) is an abnormal narrowing of the urethral lumen, causing significant restriction of urine flow from the bladder [1]. This significantly impacts the patient's well-being and quality of life [2], and leads to further complications ranging from obstructed urinary flow, acute retention of urine, recurrent urinary tract infections and calcifications, and even post-renal nephropathy in advanced cases if left untreated [3]. Causes of urethral strictures are multifactorial, encompassing iatrogenic origins in more developed countries and infective or traumatic causes in less well-resourced countries [4]. Traditional gold standard diagnostic modalities include retrograde

Cent European J Urol. 2024 doi: 10.5173/ceju.2024.121 This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0). License (http://creativecommons.org/licenses/by-nc-sa/4.0/). urethrography (RUG) and urethroscopy, allowing both radiographic and endoscopic visualisation [5]. However, RUG has been shown in multiple studies to potentially damage the urethral mucosa, over/ underestimate the length of stricture, and even potentially missing the diagnosis of a urethral stricture [6, 7]. In addition, performing the RUG requires the distal urethra to be patent for the catheter to be threaded through [8]. In this instance, the use of magnetic resonance imaging (MRI) combined with urethrograms has shown much promise both diagnostically and in surgical planning [9].

The management of urethral strictures involves a spectrum of interventions, ranging from minimally invasive techniques, such as endoscopic dilation incisions, to urethral reconstruction using tissue grafts [10]. The choice of treatment is a delicate interplay between patient, disease, and surgeon factors. Whilst traditional approaches have shown success, they may also be associated with complications, prolonged recovery periods, and even failure at times [11, 12].

There is an increasing trend in the utility of 3D imaging, artificial intelligence (AI), machine learning, and even radiomics in urology [13–15]. Machine learning-based imaging algorithms have grown leaps and bounds in recent years, showing great potential in diagnosing initially hard to spot diagnoses [16]. The ability to merge cross sectional imaging with AI to form a virtual endoscope has also aided in the diagnostic processes of many conditions [17]. With the advent of 3D imaging, accurate depiction of pathology and consequent reconstruction allows for optimal surgical planning, which would have initially been impossible without these technologies [18, 19]. 3D printing can also be utilised to accurately produce models that not just aid in the training and simulation phase [20], but the bioprinting component can also be used to replace and repair resected organs, such as the bladder in cases of cystoplasty [21].

Our scoping review aims to evaluate the recent advances in both diagnosis and management of urethral strictures, with particular focus on novel technological advancements – such as AI-powered algorithms and newer 3D imaging techniques, computerised simulation models, as well as the role of bioengineering.

Material and methods

A comprehensive literature search was carried out on 19 July 2023, by 2 independent reviewers (NHPW and KYF) across the PubMed, EMBASE, and Web of Science databases with the search terms and Boolean operators optimised to search for "Urethral Strictures", "Urethral Reconstruction", "Urethroplasty", "Artificial Intelligence", "Radiomics", "Machine Learning", "Deep Learning", "Neural Networks", "Algorithm", and "treebased" amongst others. The titles and abstracts were then screened for potential relevance, and the full texts of these articles were then further assessed for eligibility. The inclusion criteria for this review required studies to investigate or report advances in urethral stricture diagnosis or management in the fields of AI, machine learning, 3D printing, and radiomics-based applications. Studies that were non-English, case reports, abstracts only, reviews, and conference posters were excluded. The data were then extracted narratively using a standard data collection template with predefined data fields including study characteristics, objective of study, study findings, and conclusions.

Results

Search results

The search strategy yielded 1,025 articles, and after removal of 389 articles, 636 titles and abstracts were selected for screening. Twenty-five articles were assessed for full-text review, of which the final review included 12 articles (Figure 1). The included studies are shown in Table 1.

Figure 1. *PRISMA 2020 Flow Diagram.*

Table 1. *Summary of included studies*

Table 1. *Continued*

CFD – computational fluid dynamics; CNN – convolutional neural network; CT VU – computed tomography with voiding urethrography; MRVU – magnetic resonance with voiding urethrography, RUG –retrograde urethrography

Diagnostics

Artificial intelligence and machine learning

The current gold standard for diagnosing and staging USD is retrograde urethrogram (RUG) [22]. By injecting water-soluble contrast into the urethra, the urethral lumen is assessed via direct fluoroscopic imaging. It has garnered appraisal in its ability to diagnose, characterise, and localise strictures. There is currently no validated method or guideline in reviewing a RUG. In addition, the ability to accurately interpret RUG-derived images requires appropriate expertise and is operator-dependent [23]. It can also be more difficult to attain such professional opinions in often resource-scarce countries. Although endoscopic evaluation methods are also able to identify urethral strictures, they are not routinely utilised for cases with low suspicion, which may be considered as excessive to justify clinically [24]. In a bid to reduce inter-rater discrepancy, increase reliability, and reduce patient discomfort, Eun et al. [25] and Kim et al. [26] studied the ability to use AI and machine learning in the above 2 diagnostic modalities to improve and aid in the diagnostic process. Utilising the ResNet-50 algorithm, which is an AI technology based on convolutional

neural networks (CNNs), Eun et al. [25] trained the algorithm on 300 endoscopic videos (150 control, 150 strictures). With their deep learning technology and training, they were able to achieve encouraging results with 96.1% sensitivity with a false positive rate of 23.8% and a false negative rate of 2.9%. A high proportion of the false positive results were often in clinically ambiguous situations whereby the margins of the stricture were unclear. These results are encouraging and showcase the potential for deep learning technology to be used as an adjunct in objectively detecting strictures, limiting unnecessary resection of healthy tissue. Kim et al. [26] also utilised CNNs in a similar fashion using imaging obtained from RUG. With a training set of 242 RUG images (46 control, 196 strictures), the study team was able to report a high accuracy of 92.2% in the training set and 88.5% in their testing test, exemplifying a low amount of overfitting. These results, however, were only able to dichotomise whether a stricture was present or not, but were not able to determine the length, location, and potential aetiology, all of which are essential tenets of surgical management. Fan et al. [27] also showcased in their study that ultrasound images, when paired with Gabor wavelets, filters, and utilising back-propagation neural network algorithms, can accurately differentiate urethral lumen from the corpus spongiosum in normal and diseased urethras with a FPR and FNR of less than 10% and with a SI of over 90%, showing potential in the diagnostic process of urethral strictures. With the increasing application and reliable accuracy of machine learning and convolutional neural networks in diagnosing urethral strictures, there is good potential for urologists to benefit from enhanced diagnostic ability, limiting unnecessary surgical intervention.

Cross sectional imaging and virtual reconstruction

In patients with traumatic urethral strictures who are unable to tolerate the position required for RUG, there is often room to consider the use of cross-sectional imaging [28, 29]. With the advent of the virtual endoscopy [30], cross-sectional imaging can be pieced together using AI to provide an endoscopic view without the invasiveness. This not only allows for increased patient comfort, but also grants physicians the ability to appreciate precise spatial relationships of pathological regions from the images generated. In addition, RUG is not a physiological examination because the forceful pressure needed to overcome the stricture when injecting the contrast may not only flatten the stricture, but also rupture the mucosal barrier, leading to a missed diagnosis and further unnecessary complications [31].

Hanna et al. [32] examined 13 patients using 4-detector row computed tomography (4-MDCT) after they were diagnosed or suspected to have urethral strictures. The contrast was inserted into the bladder by either retrograde urethral injections, suprapubic catheter injections, or standard IV route. Whilst wearing condom catheters, the patients were told to micturate in the supine or prone position whilst the CT images over 10 seconds. The images were then reconstructed on virtual endoscopy, and the final diagnosis was compared to conventional RUG or scope, with good accuracy. The utility of cross-sectional imaging also means that lesions that were initially obscured by bony structures can also be well visualised. The authors also reported a urethral stricture surrounded by dense fibrotic tissue that was diagnosed on CT and virtual endoscopy, but not on conventional RUG. Lu et al. [33] also utilised CT imaging in patients who had either suprapubic catheter or retrograde filling of the bladder. The 80 patients were filled until they had a strong urge to void, and shots were similarly taken during urination, while the MDCT images were studied as is and with virtual endoscopic fly-through navigation software. All patients then had both RUG and flexible urethroscopy within 2 days for further diagnosis. Of all the modalities utilised, MDCT

had the highest sensitivity as it picked up 51 out of 58 of the surgically diagnosed urethral strictures as compared to the 34 diagnosed on RUG and 40 diagnosed on scope. The authors show that not only does CT scanning with virtual urethroscopy take less time than conventional scopes (8.83 ± 1.67) vs 13.55 ± 3.67 , p <0.001), but it also correlated better with intraoperative findings as compared to RUG $(0.964 \text{ vs } 0.919, \text{ p } < 0.001)$ in males.

Tsang et al. [34] studied 10 patients post high-doserate brachytherapy for prostate cancer in a bid to identify MRI radiomics features of the prostate gland pre-operatively that could predict post HDR BT stricture formation. They reported that the pre-procedural prostate gland had MRI radiomics features that demonstrated good ability in identifying urethral strictures post HDR BT. In analysis of the 3-dimensional grey-level co-occurrence matrix (GLCM) of these images, features such as lower contrast $(p = 0.04)$ and lower homogeneity (0.04) were predictive of attaining strictures after radiotherapy. Whilst this does not showcase the diagnostic ability of MRI radiomics in urethral stricture, extracting these features from the staging MRI potentially benefits prostate cancer patients by providing an additional risk stratification for patients who are more prone to developing urethral strictures. Yekeler et al. [35] also utilised MRI scans in 18 patients with 14 strictures to assess the feasibility of contrast-enhanced MR voiding urethrography (CE 3D MRVU) with consequent virtual multiplanar assessment and virtual endoscopic reconstruction. When compared to conventional RUG, the MRI was better able to pick up severe membranous strictures (which were considered as normal on RUG) with confirmation from urethroscopy. The proximal limits of the membranous strictures were also better evaluated in CE 3D MRVU than in RUG. Additionally, patients who could not undergo traditional RUG due to the mechanical obstruction from the distal strictures were able to undergo CE 3D MRVU, obtaining an accurate diagnosis. Despite a small patient group, this study showcases the advantages of MRI with 3D virtual reconstruction over traditional methods such as RUG.

Novel techniques

Cohen et al. [36, 37] studied 2 separate models and methods in identifying urethral strictures. The first was using a computational fluid dynamics (CFD) model akin to those used in cardiology [38], to assess pressure and flow parameters with different urethral stricture diseases. CFD uses complex computational and modelling techniques to analyse the motion of fluids, estimate velocity, pressure dynamics, and flow rates. In this *in vitro* study, the authors concluded that stricture size and bladder pressure both strongly impact urinary flow, whilst stricture location, length, and sequence of multiple strictures had a weaker impact. They showed that increasing the stricture size from 15 Fr to 10 Fr decreased the mean velocity from 315.8 mm/s to 177 mm/s, and the flow from 24.8 ml/s to 13.8 ml/s. It is of note that CFD faces the same limitation as other non-invasive measurements like PVRU and uroflowmetry in the sense that it does not differentiate neurogenic bladders from a bladder outlet obstruction. Whilst their study did not account for the elasticity and shape of a true urethra, and the external compression of the prostate was also not accounted for, but their model demonstrates that flow rates from the CFD model were consistent with the uroflowmetry values found in the literature and could potentially be used as an adjunct for research and clinical practice. In a study published in 2020, Cohen et al. [36] also studied in a separate *in vitro* model the urinary spray patterns of various normal and abnormal anatomical conformations of the urethra. Despite identifying that urinary occlusion in the case of strictures leads to slow relative flow rate and could significantly increase the diameter of spray $(p = 0.03)$, they did not report an *in vivo* extension to diagnosing urethral strictures in humans. The findings from this study, coupled from the initial CFD study, could potentially come together to help urologists understand the confluence of dynamic flow and spray pattern in urinary diseases in identifying urethral strictures. When used as an adjunct to other investigative methods such as RUG, it could help in diagnosing and prognosticating disease burden.

Management

Pre-operative planning using 3D models

Urethral reconstruction is a highly intricate surgical procedure necessitating meticulous preoperative planning due to the minute and intricate anatomy of the urethra and the variability in patient presentations. The success of urethral reconstruction relies heavily on accurate and precise identification of the structured or injured segment, preservation of surrounding structures, and restoration of urethral continuity whilst avoiding periurethral injury [39]. Zhang et al. [40] showcased in their *in vitro* study that 3D-printed urethral models in the context of pelvic fracture urethral injury (PFUI) have good potential in helping clinicians plan preoperatively. The authors assessed 3 separate patients with PFUI,

and utilised 3D reconstruction software to print 3D anatomical models based on CT-attained imaging. The polycaprolactone (PCL) models took 5 hours to print on average and were evaluated subsequently with stellar results by both patients and clinicians. The former reported that when compared to other imaging modalities such as urethroscopic images or CT images, the models were easier to understand and contributed significantly to their level of disease awareness. Clinicians found that, subjectively, these models were the best in reflecting the relationship between the proximal urethra and pubic symphysis, as well as the urethra and the rectum, which are both important surgical considerations. Whilst they did opine that the models were not better in evaluating length of urethral stenosis and disease, objective measurements of disease anatomy and extent were similar between the model and intraoperative findings. Similarly, Joshi et al. [41] utilised acrylic fibres to reconstruct and print 3D printed models of 10 different patients with PFUIs. Similarly, the models were shown to help understand the anatomy of the posterior urethra, and they depicted the exact displacement of the posterior urethra, its relationship to the pubic bone anterior and the rectum posterior, its relative displacement from the midline, and the status of the anterior urethral wall. Field experts such as practising urologists and fellows subjectively reported that these models were useful in helping them make peri- and pre-operative assessments, especially with regards to the need to perform an inferior pubectomy to bridge the gap between the 2 ends of the urethra. Utilising these models to plan preoperatively has also been reported to shorten surgical time. The status and accuracy of 3D models printed using CT-attained imaging gives an insight into the potential use of 3D models for preoperative planning as well as patient disease education.

Bioengineering urethral tissues

Accurate diagnosis and good pre-operative planning, as previously mentioned, are all important cornerstones in the journey of the patient with a urethral stricture. The successful outcome of the patient thereafter lies in the hands of a good surgical repair alongside adequate urethral reconstruction. The latter often is done by utilising substitute materials such as an autologous penile flap or mucosa from the buccal [42–44], which often come at the expense of significant risk of damage or true damage to the donor site, such as, but not limited to, bleeding, infection, nervous injury, cosmetic injury, and even functional limitations. Hence, there has been a rapid development in the utilisation of tissue bioengineering and regenerative medicine as an alternative approach. In the realm of 3D-based applications, Zhang et al. [45] showed that 3D bioprinting technology using CT-obtained images can fabricate urethras *in vitro* using PCL and polylactide-co-caprolactone (PLCL) polymers in a spiral scaffold design to mimic the structural and mechanical properties of urethras in rabbits. The authors also showed that cell-laden fibrin-based hydrogens, when used on the 50/50 PLCL polymers in a spiral design, had a highly suitable and optimal microenvironment for bladder cells and smooth muscle cells to be viable, to proliferate and to express cell-specific biomarkers overtime, allowing for potential future expansion into human use. Huang et al. [46] also showed that urethral reconstruction using a novel 3D porous bacterial cellulose scaffold seeded with rabbit lingual keratinocyte had good potential when compared to other techniques in formulating urethras that maintained their inner calibres without reforming strictures over time. Collagen-based tubular scaffolds, when used in the context of urethral bioengineering, have also been shown to have sufficient intrinsic radial elasticity that is potentially useful in the regeneration of dynamic tubular organs such as the urethra [47], with the potential to remain functional for at least 6 years in the clinical setting [48].

Discussion

Diagnostics

Urethral stricture disease presents a significant challenge in the field of urology, affecting patients' quality of life as well as potentially leading to severe complications if left untreated. Traditional diagnostic modalities such as RUG and urethroscopy, whilst effective, have limitations including operator dependency, invasiveness, and the potential for missing or misdiagnosing strictures. However, recent advancements in AI, machine learning, radiomics, and imaging technologies, as discussed above, offer promising solutions to enhancing diagnostic accuracy and patient outcomes. The integration of AI and machine learning algorithms into diagnostic processes has already shown encouraging results in improving the interpretation and accuracy of imaging modalities such as RUG and ultrasound. With deep learning algorithms already shown to reduce operator dependence and inter-rater variability in other fields [49, 50], urologists can also benefit greatly from these in the field of strictures. A paradigm shift towards more objective and reliable diagnostic methods can ultimately benefit patients by minimising unnecessary interventions and by optimising treatment planning.

Furthermore, cross-sectional imaging techniques when combined with virtual reconstruction can offer non-invasive alternatives to traditional diagnostic procedures, especially with patients who may not tolerate invasive techniques or those with complex anatomical and surgical considerations. With early studies showing keen progress in the utility of CT imaging and virtual endoscopy in visualising urethral strictures when compared to traditional and conventional RUG, patients can potentially benefit in the long run by reducing unnecessary exposure to sedation risks and procedural risks. Additionally, the ability of MRI radiomics and features on early cross-sectional imaging to provide valuable insights into predicting post-therapeutic outcomes and assessing the severity of strictures allows clinicians to better stratify and counsel patients on their potential outcomes.

Management

Education via models, ranging from standard silicone models, custom printed metal implants, and even 3D-printed replicas, have been shown in various fields to improve patient education and satisfaction [51–53]. In addition, 3D modelling techniques have also been shown to offer invaluable tools for perioperative surgical planning and assessment, especially in regard to anatomically challenging and non-standard cases [54–58]. Studies by Zhang et al. [40] and Joshi et al. [41] showcased the efficacy of 3D-printed models in facilitating surgical planning in the setting of urethral strictures, as above. Further cohortbased prospective studies can help us gain better insight into the extent of benefits in both patient and surgical outcomes of these printed models.

The emergence of bioengineering and regenerative medicine also presents promising avenues for tissue reconstruction in the realm of urethral strictures. The ability to create patient-specific biomimetic tissue constructs that closely resemble native tissue architecture and function holds great promise because it allows for tailored interventions that address individual patient's needs and minor anatomical variations [59]. Additionally, the potential for enhanced biocompatibility means reduced immunogenicity and improved interaction with host tissues as compared to traditional graft materials. The ability to minimise donor site morbidity and eliminate the need for secondary surgical procedures to obtain or fix these grafts are also of great benefit to patients. In orthopaedics, 3D-printed implants and scaffolds have already been used to regenerate bony tissue in patients with bone defects and fractures [60–62]. Similarly, tissue-engineered heart valves and patches have shown great results in restoring cardiac function and fixing valvular abnormalities in the realm of cardiothoracic surgery [63–65]. The integration of bioengineering and regenerative medicine principles holds tremendous potential in revolutionising the field of stricture management, offering innovative solutions that improve outcomes whilst reducing risks for this debilitating condition. Further research is required to optimise tissue engineering techniques, validate their efficacy in clinical trials, and ensure their safe implementation into routine urological practice.

Current limitations and future directions

The implementation of advanced technologies such as artificial intelligence, machine learning, radiomics, and 3D printing may face significant challenges related to cost, infrastructure, and expertise, particularly in resource-limited settings across the world. Future studies should include centre-based cost analyses to assess suitability. Additionally, the included studies primarily focused on specific aspects of urethral stricture management and diagnosis but did not report certain important aspects such as patient-reported outcomes and cost effectiveness. Most of the studies were also observational retrospective studies or experimental in nature, which lacks robust clinical validation in diverse patient populations. Future research should hence aim to address these gaps with more comprehensive reviews and randomised controlled trials. Large-scale, multicentre studies are needed

to validate the efficacy, safety, and cost-effectiveness of these novel technologies and interventions. It is envisioned that with further development and availability of these advanced technologies, urethral strictures will be a condition that is readily diagnosed and managed with optimal patient outcomes and prognosis.

Conclusions

Our scoping review underscores the transformative potential of innovative technologies in advancing the diagnosis and management of urethral strictures. Recent advancements in AI, machine learning, 3D printing, and radiomics offer promising avenues for enhancing diagnostic accuracy and reliability over traditional methods. Cross-sectional imaging techniques, when coupled with virtual reconstruction, also provide non-invasive alternatives whilst providing prognosticating insights. Additionally, 3D printing and bioengineering approaches hold promise for personalised interventions with reduced site morbidity.

Conflicts of Interest

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

Approval of the Bioethics Committee was not required.

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