Urovision 2020: The future of urology

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ABSTRACT

Urology, as a specialty, has always been at the forefront of innovation and research. Newer technologies have been rapidly embraced and, in many cases, improved upon in order to achieve better patient outcomes. This review addresses the possible future directions that technological advances in urology may take. The role of further miniaturization of urolithiasis treatment, robotic surgery and other minimally invasive techniques is addressed. The potential for enhanced imaging and diagnostic techniques like magnetic resonance imaging and ultrasonography modifications, as well as the potential applications of nanotechnology and tissue engineering, are reviewed.

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Keywords: Future of urology, imaging techniques, nanotechnology, targeted therapy, technology

INTRODUCTION

From the humble beginnings of uroscopy and catheterization, urology today is practically unrecognizable.[1] Even stalwarts like Hugh Hampton Young or Charles Huggins would have had difficulty foreseeing the mind-boggling developments in the specialty. Technological advancements are occurring on a day-to-day basis, and it would be worthwhile to look at some that have the potential to alter urological practice.

Management of urolithiasis

Smaller, flexible ureteroscopes have revolutionized the management of renal calculi.[2] The use of charge-coupled devices and complementary metal oxide–superconductor technology in digital ureteroscopes has improved vision and reduced surgical time.[3] This was demonstrated by Somani *et al.*, who, on comparing digital and conventional ureteroscopes, found a significant reduction in operative time in tackling calculi with the digital ureteroscope.[3]

As technology improves, it seems likely that a substantial proportion of stone disease will be tackled by this approach. Its low morbidity, combined with improving stone-free rates (by using newer baskets and gels to prevent retropulsion), makes it an attractive option for both physicians and patients.[2] Familiarity with the technique and improved durability of instruments will reduce the cost, which still prohibits its routine use in developing countries.

Miniaturization has been applied to percutaneous renal stone surgery. Mini-perc involves the use of tracts less than 20 French, and is gaining popularity for renal calculi 1-2 cm in size.[4] Sabnis *et al*. demonstrated a 100% clearance for 1-2-cm-sized stones using this technique.[4] More head-to-head comparisons between mini-perc and digital ureteroscopy will help establish the modality of choice.

Micro-perc uses an all-seeing needle with a tract size of just 4.85 French, and has been used for renal and bladder calculi.[5] Dilatation is achieved in a single-step and a slender 200 micron LASER fiber is used for stone fragmentation. Desai *et al.*, have reported the initial experience and have demonstrated a favorable clearance rate with minimal morbidity.[5]

The minimally invasive nature of these modifications with reduced blood loss and improved stone clearance make them an attractive option. A recent review on the future of shockwave lithotripsy concluded that unless future

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modifications allow complete disintegration in a single session, it is likely that patients and physicians will prefer endourological approaches.[6] Some of these modifications include the use of a dual EHL system or double-layer arrangement of piezo-electric elements for fragmentation, adaptation of the focal zone to the stone size and the use of broad-focus low-pressure lithotripters.[6]

Robotic surgery and other minimally invasive technology

Urology has been at the forefront of robotic surgery since its inception. Radical prostatectomy is one of the most commonly performed robotic procedures, and robotic surgery has been proven as an alternative to open and laparoscopic radical prostatectomy.[7] There has been an expansion of urological procedures that are being performed using robotic equipment, with the visualization and ease of suturing in the limited space of the pelvis, proving a specific advantage. Ghani *et al.* recently demonstrated the feasibility of robotic anatrophic nephrolithotomy.[8] Other surgeons have described the expanding indications of robotic procedures in pelvic organ prolapse repair and urinary tract reconstruction, including ureteric reimplantation.[9-11] Yates *et al.* described robot-assisted implantation of an artificial urinary sphincter in six patients with incontinence of urine secondary to neurogenic lower urinary tract dysfunction.[12] Robotic surgery in infants and toddlers is gaining acceptance.[13] In a series of 65 procedures in children under the age of 3 years, Srougi *et al.* demonstrated no conversion to open surgery, and concluded that any technical limitations to robotic surgery could be overcome with specific maneuvers and training.[13]

Oncological procedures including cystectomy with intra-corporeal reconstruction and partial nephrectomy are being regularly performed using robotic assistance.[14,15] In a comparison between laparoscopic and robotic partial nephrectomy, Faria *et al.* demonstrated that the robotic approach was associated with a significantly rapid suturing time, thereby reducing the warm ischemia time by an average of 7 min.[14] Kader *et al.* have shown significantly lower morbidity with comparable oncological outcomes when comparing robotic and open radical cystectomy.[15]

The 3-D view and elimination of tremor make robotic surgery uniquely suited to micro-surgical applications. Parekattil *et al.* reviewed preliminary studies of robotic micro-surgical procedures like vaso-epididymostomy and denervation of the spermatic cord, and concluded that operative efficiency was increased and success rates were equal in these small studies.[16]

Clearly, the potential for expansion of robotic surgery in urology is vast and larger studies will determine the exact role. The prohibitive cost of robotic surgery remains an issue, and critics point out that there is no proven long-term advantage over traditional forms of surgery. However, with the patents of the market leader scheduled to expire by 2016, and alternative systems being developed by rivals, there is a strong possibility that a cost-reduction would occur, allowing widespread penetration of the technology.[17,18] Further research has begun into how best to incorporate haptic feedback into the robotic system enabling the surgeon to "feel" during the procedure, thereby eliminating the disadvantage of "sight-only" feedback of traditional robotic systems.[19]

Minimally invasive techniques like cryoablation, radio-frequency ablation and high-intensity focused ultrasound (HIFU) will also be refined, allowing better oncological outcomes and expanding their indications. Atwell *et al.* showed excellent recurrence-free survivals in cases of renal masses < 3 cm in size, with both cryo- and radio-frequency ablation.[20] The INDEX study is a multicenter prospective study planned to evaluate the outcome of HIFU in treating low- to intermediate-risk localized prostate cancer.[21] This study will give us an idea of the feasibility of organ preservation using these minimally invasive technologies. Newer generation equipment has improved the safety and efficacy of these systems and their potential is huge, especially in the ageing population, with significant comorbidities who may be unsuitable for more radical therapies.

The operating room of the future promises to be radically different from what we know today. Bharathan *et al.* predict that use of computer-based surgical platforms like robotics, combined with improved navigation and surgical precision through the development of nanomedicine, along with the integration of various operating room functions, will become a reality.[22] Intra-operative combination with augmented reality navigation systems has been used to assist surgical resection in renal and adrenal tumors.[23] These new technologies hold the potential for drastically altering urological surgery.

Imaging and diagnostic tests

Urologic imaging at present is dominated by computed tomography (CT), but the coming decade could see the rise of magnetic resonance imaging (MRI) and ultrasound (US).

While MRI is the most important modality in prostate cancer staging, the present sensitivity and specificity is not ideal, with hemorrhage, infection, fibrosis, atrophy and post-treatment effects remaining confounders.[24] Recent modifications of MRI have proven valuable in multi-parametric imaging of prostate cancer.[24]

Diffusion-weighted MR (DWI) measures Brownian motion of water molecules and can differentiate benign from malignant tissue and hemorrhage from neoplasia, and identifies areas of higher Gleason grade within a cancer.[24] Malignant lesions have been found to have lower ADC values than benign tissue, and these values decrease with worsening of the Gleason grade.[24] The addition of DWI has been found to increase the sensitivity (54-98%) and specificity (58-100%) of detection of prostate cancer, and helps in categorizing its aggressiveness.[24]

MR spectroscopy (MRS) or chemical shift imaging allows detection of the chemical environment in tissue.[24,25] The chemical fingerprint is used to differentiate areas suspicious for malignancy. In the areas of a cellular tumor with increased membrane turnover, the choline signal is increased, allowing localization of prostate cancer.[24] The citrate peak of normal prostate tissue is reduced in cancer.[24] However, both these observations can also be seen in prostatitis or hemorrhage, reducing the specificity of the technique.[26] Strong signals from the surrounding BPH, or even normal tissue, can obscure small cancers, reducing the sensitivity of MRS.[24,25] Combination with other MRI parameters has increased the detection of prostate cancer, been used to guide biopsies and improve tumor volume estimation.[24,25]

Dynamic contrast-enhanced (DCE) MRI relies on increased tumor vascularity with hyper-enhancement and rapid washout used to identify malignancy. It has been shown to nearly double the detection of malignancy in men with raised prostate-specific antigen (PSA) and prior negative biopsies (46% versus 24%) when used in combination with MRS.[24] It improves staging accuracy. However, a consensus for cut-offs needs to be reached.[24] False positives from prostatitis and false negatives from prostatic intra-epithelial neoplasia have been shown to occur.[24] Further refinements in technique and interpretation will allow more widespread utilization.

The3-Tesla MRI allows better spatial resolution and its increased signal–noise ratio enables better detection, localization and staging of prostate cancer while eliminating the need for an endorectal coil.[24] Newer techniques like MRS, DWI and DCE-MRI also benefit significantly from the 3-Tesla coil. The combination of MRS and DCE-MRI with conventional T2-weighted imaging (all using the 3-Tesla coil) has shown higher specificity (97% vs 85%) than T2-weighted imaging alone, and also improved the accuracy and predictive value for localization of prostate cancer.[24]

The development of MRI-guided biopsy and MRI-US fusion biopsies also holds potential.[24] The detailed anatomic visualization possible using MRI allows better targeting of biopsies. A number of techniques have been described.[24] Of these, the MRI-compatible “stealth” robot appears to be most promising, and has been shown to be accurate to within 0.3 mm in a dog model.[24] The maturation of this technology, in combination with research to define indications, will allow the development of a clear diagnostic algorithm for localized prostate cancer.

MRI techniques have been studied in other urological diseases. Contrast-enhanced MRI and DWI have been shown to distinguish muscle-invasive from non-muscle-invasive bladder cancer with an accuracy >80%.[24] DWI can also potentially distinguish benign from malignant tissue and grade bladder malignancy.[24] Small studies have also shown its ability to determine the response of bladder malignancy to chemotherapeutic agents.[26]

DWI has been used to distinguish subtypes and grades of renal carcinoma (RCC), characterize complex cysts and distinguish benign from malignant tumors.[27,28] In a study of 105 patients, Inci et al. determined that the ADC value of solid tumors was significantly lower than normal renal parenchyma or renal cysts.[27] They further demonstrated a significant reduction between Bosniak II–III and Bosniak I cysts. Goyal *et al.* also demonstrated significant reduction in ADC values in patients with increasing nuclear grade of RCC, and showed that clear cell RCC had a higher ADC value than non-clear cell RCC.[28] Such determinations and the identification of cut-off values could help grade and characterize the tumors before surgery, allowing risk-stratification and appropriate management of small renal masses. Contrast-enhanced MRI and MRS have been studied in the differentiation of benign and malignant renal tumors, and may offer a method of differentiation of oncocytoma from RCC.[29]

MR urography combines exquisite anatomical delineation with a functional estimation that is potentially less affected by reduced renal function thus allowing complete evaluation of upper tract obstruction.[30] Jones *et al.* calculated time intensity curves and transit times for MRI, akin to functional nuclear imaging, and were able to identify obstructed systems.[30] They further correlated possible causes of pelvi–ureteric junction obstruction with their functional parameters, and concluded that MR urography could help in further clarifying the pathophysiology of the disease.[31]

US too is showing promise. Uses of contrast-enhanced US (CEUS) include detection of prostate cancer with targeting in patients with previously negative biopsies. Cornelis et al. demonstrated a pick-up rate of 30.9% in biopsies targeted by CEUS.[32] PSA levels and Gleason scores correlated with the positivity of biopsies.[33]

CEUS allows better characterization of complex renal cysts and Siracusano *et al.* concluded that it allows a good alternative to CT, especially in cases of contrast allergy.[34]

Power Doppler, harmonic and flash replenishment, Histoscanning, 3D reconstruction and elastography are modifications of ultrasound that have been used with some success at targeting prostate biopsies and increasing detection following previously negative biopsies.[33] They can identify residual tumor after radiotherapy.[33] Power Doppler may also increase the accuracy of detection of extra-prostatic tumor extension.[35] Zalesky *et al.* demonstrated an excellent predictive value for extra-capsular extension of 3D-Power Doppler in 146 patients with clinically localized disease who underwent radical prostatectomy.[35]

The improved imaging characteristics of MRI and US, combined with a lack of ionizing radiation, will prove major advantages in the decade ahead.

Narrow band imaging (NBI) is a technological advance whose impact in the management of bladder cancer will be visible in the next few years. It is safe, can be performed for diagnosis or resection, has limited initial cost and does not require additional materials.[36] A large meta-analysis by Zheng *et al.* revealed increased sensitivity and diagnostic accuracy versus traditional white-light cystoscopy.[37] It also proved very sensitive in the diagnosis of carcinoma *in situ*, which is a limitation of traditional cystoscopy.[37] Results of larger trials will be available soon, and any technique likely to reduce the cost associated with surveillance of bladder cancer by decreasing recurrences will potentially have a significant role in its management.

NBI has also shown promise in the detection of upper tract malignancies.[38] Meyer *et al.* reported an increased detection rate of 14.2%, with further 8% patients showing a widening of margins following NBI use.[38]

Techniques like Raman spectroscopy, optical coherence tomography and confocal laser endomicroscopy are new techniques that use the interactions between light and tissue to characterize structural changes in the tissue.[39] Raman spectroscopy, especially, has shown potential in identifying specific markers of malignancy, and could be used as a tool for the early detection of cancer.[39] Further studies are required. However, these new techniques hold the promise of obtaining histopathological and microscopic information using a cystoscope.

Molecular imaging refers to the use of molecular probes in combination with optical or fluorescent techniques to functionally image malignant tumors.[23,40] In combination with MRI, CT, positron emission tomography and single photon emission CT, they have the potential to improve staging.[40] Macis *et al.* reported an experimental study using a molecular probe, BR55, to target prostate cancer cells as well as the antibody to carbonic anhydrase IX to target clear cell RCC.[40] They believe that advances in technology could lead to early diagnosis and individualized treatment in these patients.

Nanotechnology

Nanoparticles are materials of size 1-1000 nm with various biomedical applications.[41] At this scale, the interaction of materials with tissue changes due to the surface area–volume ratio.[41] Nanomedicine explores the potential applications of these materials in the diagnosis and treatment of disease and even the potential replacement of tissue function.[41]

The best-studied application of nanoparticles is their use as carriers for medications, allowing better penetration with lower toxicity. This has particular use in intravesical therapy for bladder cancer, where their combination with chemotherapeutic agents has been studied, especially *in vitro*.[42] McKiernan *et al.* reported a phase I trial on 18 patients using nanoparticle albumin-bound paclitaxel in patients refractory to BCG.[42] Toxicity was minimal and the response rate was about 28%, prompting a larger phase II trial.[42] In prostate cancer, nanoparticle-coated docetaxel and thermotherapy with para-magnetic nanoparticles have been studied with promising results *in vitro*.[43,44] Luo *et al.* demonstrated oleic acid-coated hydroxyapatite nanoparticles loaded with docetaxel, induced apoptosis through additional mechanisms. This indicated that nanoparticles may have biological effects and may not be simple passive carriers.[43] Johansen and colleagues demonstrated the feasibility of thermotherapy with para-magnetic nanoparticles in 10 patients with recurrent prostate cancer.[44] In rabbits, silver hydroxyapatite coatings were found to significantly reduce bacteriuria and following indwelling catheterization for 1 week.[45] Proof in humans would help achieve a safe and effective method of reducing colonization from indwelling catheters or stents.

The use of lymphotropic para-magnetic iron oxide particles has greatly improved the sensitivity for detection of lymph node metastases in urological cancers, especially bladder and penile cancer.[46] Para-magnetic iron particles were shown to be nearly 100% sensitive in the detection of involved lymph nodes in prostate cancer.[24] Larger studies and better availability of these agents are pre-requisites to widespread use.[46] Quantum dots are fluorescent nanometer probes used for molecular imaging of malignancy.[41] Nanoparticles are being studied for the detection of single nucleotide polymorphisms (SNP's) in genetic diseases and as nanowires for the identification of bacteria.[41]

Tissue regeneration remains the holy grail of reconstructive surgeons. This is exemplified in urology because of the unique anatomical, physiological as well as pathological processes involved. Atala *et al.* described their initial experience with the use of autologous stem cells as bladder substitutes in children with improvement in bladder volume and compliance.[47] Subsequently, animal studies involving replacement of the penile urethra using autologous stem cells seeded in tubularized collagen matrices showed good results for long-segment strictures.[48] The injection of muscle precursor cells into irreversibly damaged sphincters in dogs also showed promise.[49] Nanoparticle-based scaffoldings have been developed and provide an added dimension in tissue regeneration by regulating and promoting intimate cell-substrate interactions.[50] Recently, researchers have also described initial results using rat neonatal kidney cells and three-dimensional scaffolds in an effort to develop an artificial kidney.[51] Collaboration between the fields of nanotechnology, regenerative medicine and bioengineering could hold the key in making the dream of tissue replacement a reality.[52]

CONCLUSION

The future of urology remains extremely exciting. Miniaturization, optical technology and robotics constitute the future of surgery. The use of state of the art imaging that avoids radiation exposure has the potential to revolutionize diagnostics. There is even a real possibility of tiny nano-bots and nano-biotics coursing through the bloodstream to their targets. Science fiction writers could not have done better! However, a note of caution would be appropriate here. While it is easy to be swept away in this storm of technology, we must not become slaves to it. Clinical acumen and rational judgment, always keeping the patient's interests at heart, remain essential to the practice of the art of medicine. We must never allow Albert Einstein's prophetic words uttered nearly a century ago to apply to urology, "*It has become appallingly obvious that our technology has exceeded our humanity."*

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