World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-15, October 2022
ISSN: 2749-3644

WORLD-CLASS NEW TECHNOLOGIES IN THE TREATMENT OF URINARY DISEASES

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Article history:

Received: August 24th 2022
Accepted: September24th 2022
Published: October 30th 2022

Abstract:

Since prehistoric times, our understanding of urology has rapidly expanded. Whilst primitive urologists began by using urine as a therapeutic substance, modern urologists may find themselves removing a kidney remotely by driving a robotic arm, with seven degrees of movement, while using image overlay-augmented reality. This review provides an insight into the potential status of urological technology in 20 years' time, assessed through an analysis of developments in imaging, diagnostics, robotics and further technologies. A particular emphasis is given to the promising fields of minimally invasive techniques, nanotechnology and tissue engineering, which likely hold the key to a new era for urology.

Keywords: Diagnostic tools, future technology, imaging, robotics, urology

Since prehistoric times, urology has fascinated humans, from observing urine and its potentially healing properties, to the utilization of reeds to alleviate bladder obstruction.[1] Thousands of years later, armed with an increased knowledge of anatomy and medicine, urological practice is at a stage where the majority of effort is put towards producing technology that offers a minimally invasive, individualized and targeted approach to treating disease.

This paper seeks to identify, in this rapid evolutionary stage, where urological technology will be by 2038. Herein, imaging and diagnostics, robotics and new, upcoming technology will be considered. However, as urology is a field at the forefront of research and innovation, it is only possible to provide a glimpse into current developments.[2]

IMAGING AND DIAGNOSTICS

In 20 years' time much will have changed in imaging and diagnostics, including both an improvement in the scope of current technology, and the utilization of new techniques currently under development. Narrow band imaging (NBI) is just one of these new techniques, using specific blue and green wavelengths in endoscopy to enhance mucosal detail.[3] NBI has a greater ability to detect cancerous tissue compared with the currently prevalent white-light cystoscopy, with research finding that the use of NBI in transurethral resection of bladder tumours reduced tumour recurrence.[4] Whilst this imaging may benefit those with nonmuscle invasive bladder cancer, it may have further ramifications for other urological cancers.

The use of magnetic resonance imaging (MRI) in diagnosis will also be improved through pioneering nanotechnology, including the attachment of magnetic nanoparticles to specific targets, such as lymph-node metastases, which can then be visualized on MRI.[5] In addition, MRI has been found to be significantly better than prostate-specific antigen (PSA) measurements in the follow up of patients after focal therapy for prostate cancer.[6] Furthermore, through multi-parametric imaging, MRI–ultrasound fusion in prostate biopsy is showing great promise with real-time ultrasound imaging to better sample the prostate to improve Gleason score.[7,8] In the future, with the possible reduction in cost of MRI scans, these techniques may become more widely utilized.

Recent advances in MRI technology have also yielded the 7 Tesla MRI, which boasts a major improvement in diagnostic technology over the current 1.5 and 3 Tesla models. Through enabling an increased spatial resolution and enhanced vessel signal, the system allows for superior diagnostic quality, providing more accurate identification of abdominal pathology, such as in the prostate.[9] Enhanced detection of prostate cancer recurrence has also become possible through the identification of the prostate-specific membrane antigen (PSMA) expressed by almost all prostate cancers.[10] This antigen is hoped to allow replacement of the currently used ^{18}F-flurocholine positron emission tomography (PET)/computed tomography (CT) by ^{68}Ga-PSMA-11 PET/CT, which is noted to be superior in identifying prostate cancer recurrence and extra prostatic disease.[11] Furthermore, recent studies suggest that due to its high sensitivity and specificity, there may be added benefit in the use of ^{68}Ga-PSMA-PET/CT in primary staging for metastatic spread.[12] It is hoped that through a multicentre prospective clinical trial, ^{68}Ga-PSMA-PET/CT can be directly compared with

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conventional scans to better understand if the method has improved diagnostic ability in primary staging, with subsequent positive effect on patient management.[13]
In addition to PET/CT, current studies suggest that the PSMA PET/MRI offers even further advantages by identifying lymph-node metastases that would have been missed on CT.[14] This method of PSMA PET/MRI has been seen to be particularly useful when PSA levels are low, showing a high detection rate for locally recurrent disease.[15] In addition, PSMA has further theranostic applications in local salvage therapy, such as in the use of lutetium-177-labelled PSMA (^{177}Lu-PSMA), which directly treats prostate cancers with the added benefit of a reduction in side effects.[16] Beyond local therapy, treatment with ^{177}Lu-PSMA has also been seen to have high response rates in patients with PSMA-avid metastatic prostate cancer that is castration resistant.[17] However, more research and study is required before this practice becomes regularly used, and it is likely that in the next two decades more specific ligands will be found to enable a more personalized treatment approach for all, potentially acting as a key to theranostic urological advancement.
Beyond imaging, 'tumour markers' are likely to become more sophisticated. Two recently found markers for monitoring oncological burden are serum microRNA and circulating tumour cells (CTCs). CTCs, first identified by Ashworth, have recently been found to best predict patient survival in metastatic castration-resistant prostate cancer, with low levels indicating a good prognosis.[18,19] Furthermore, through genomic analysis of the cells, CTCs have utility in the identification of specific therapeutic targets for tumours.[20] In addition, the specific microRNA, miR-371a-3p, is a novel biomarker recently found to be both sensitive and specific for testicular germ-cell tumours, more so than the blood tests currently used in diagnosis.[21,22] These tumour markers, as well as the newly found ability of dogs to smell the urine of patients to identify prostate cancer, highlight the potential ease of screening and monitoring of patients in the future and helping 'personalized medicine' based on genomics to flourish

ROBOTICS

Urology pioneers progression in the field of robotics. Robotics has been adopted because of it being minimally invasive, providing 3D vision, allowing magnification of fields of view and providing enhanced precision and dexterity.[24] However, well-documented problems in current robotics include the external clashing of instruments, lack of haptic feedback and difficulty in maintaining triangulation around the surgical field. Thus, a new single-port platform has been adapted for use in robotics, utilizing only one entry site into the patient. This single port can accommodate a camera and multiple robotic instruments, whilst only requiring one arm of the da Vinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA). Furthermore, the instruments within the port have an elbow joint, providing increased intracorporeal triangulation for better dexterity.[24] In a clinical trial on 19 patients, this single-port technique proved to be successful.[25] Further improvements to current robotics that may be seen include hydraulic manipulators with built-in sensors to improve tool precision, and Firefly® technology (Firefly Technology, Winchester, UK) to better guide tumour resection in a partial nephrectomy.[26,27]
New robotic procedures are also likely to be implemented in the future. In an effort towards complete tumour removal without incision and scattering, novel procedures may include a robotic *en bloc* resection for nonmuscle invasive transitional cell carcinoma, as well as a robotic radical prostatectomy with a perineal approach.[28–30] In addition, future advances in robotics such as the Telelap ALF-X (Intuitive Surgical Inc.) improve upon the artificial da Vinci surgical environment by increasing situational awareness of surgeons through the use of 3D glasses, as opposed to enveloping the surgeon's face, whilst also providing haptic feedback technology.[31]
Robotics is likely to become available to all patient cohorts, contributed in part by the expiration of a number of intellectual property patents, and thus a reduction in costs.[32] In addition, as highlighted from a recent review on 65 children, robotics is gaining increased acceptance in paediatric urology. Despite obvious challenges due to the smaller and more complex anatomy, technical manoeuvres, such as decompression of the bladder, can be learnt to overcome these obstacles.[33]
The future of robotic urological surgery is exciting and will improve postoperative outcomes and patient satisfaction[28] However, it demands greater complexity in terms of structural needs, staff and technology, and therefore must be constantly scrutinized.[34] In addition, robotic surgery has not been proven to be better than laparoscopic surgery in many procedures such as radical nephrectomy, indicating that more improvements still need to be made, particularly in a healthcare system with limited resources.[35]

MINIMALLY INVASIVE TECHNOLOGY

In an age where techniques are being refined to offer reduced infection rates and length of hospital stay, minimally invasive treatments will surely become increasingly used over the next 20 years. For example, current data on cryotherapy ablation in prostate cancers that uses precise mapping and biopsy has

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been promising, although more trials are still required.[36] It is likely that computer and robotic-assisted methods will help revolutionize cryotherapy and take it to new heights.[37] In addition, the method of radiofrequency ablation (RFA) for renal cancer has been seen to be safe and effective, especially for those patients in which surgery will not be tolerated.[38] RFA also offers the advantage of better outcomes, compared with partial nephrectomy, whilst preserving more renal tissue.[39] Importantly, however, RFA has not been seen to be suitable for all tumours, with lesions greater than 5 cm having a high failure rate; future advances will likely improve upon this.[38,40]

A final ablative treatment to be considered is high-intensity frequency ultrasound (HIFU), which may become of use in salvage therapy for prostate cancers that recur following radiotherapy.[41] This method reduces complications associated with salvage prostatectomy, whilst conferring good clinical outcomes. The procedure will likely be benefited, over the next 20 years, by the use of simultaneous imaging such as ultrasound, a process that provides real-time quality feedback on the HIFU procedure.[41,42]

It is also clear that minimally invasive techniques hold the future for the management of urolithiasis, with a notable increase in the use of ureteroscopy and percutaneous nephrolithotomy (PCNL), and a concurrent reduction in the use of open surgery over the past few years.[43] In addition, it is likely that these current techniques will be further improved upon, with methods such as the concurrent use of the Uro Dyna-CT (Siemens Healthcare Solutions, Erlangen, Germany), which creates real-time cross-sectional and three-dimensional images that help to improve the PCNL process, whilst also conferring improvements in stone-free rates after the procedures.[44]

Furthermore, the PCNL process has evolved since its conception in 1976.[45] As well as the aforementioned advancements imaging will likely add to the technique, many companies have allowed for miniaturization of the equipment used, which has helped to reduce complication rates, whilst providing an increased ability to access difficult stones in all populations.[46–48] Thus, in the next two decades it is likely that these miniaturized PCNL techniques will hold the key to stone management.

A NEW AGE

With benign prostatic hyperplasia and obstruction becoming more prevalent in our increasingly ageing population, it is becoming increasingly important to find improved treatment techniques.[49] Possible new techniques of management, which have the potential to replace transurethral resection of prostate (TURP) and open prostatectomy, are holmium laser enucleation of the prostate (HoLEP) and thulium vaponucleation. Both these methods have shown equal clinical efficiency and safety in treating benign prostatic obstruction.[50] Furthermore, recent studies suggest that modified HoLEP with preservation of urethral mucosa may allow for patients to leave hospital within the day, thus further improving patient standards of care.[51] It is however noted, that although current operative time with thulium vaponucleation compared with TURP is longer, it is hoped that with time technique refinement can occur.[52] One additional management technique to be considered for benign prostatic hyperplasia is prostate artery embolization. This promising method, which involves the therapeutic occlusion of arteries supplying the prostate, has been seen to be a safer alternative to minimally invasive methods such as HoLEP, and can be performed as an outpatient.[53] However, before the therapy can be used as standard, further patients will need to be studied in future trials to better analyse complications and clinical benefit.[54]

In addition, with chronic kidney disease becoming more prevalent, it appears tissue regeneration will be a cornerstone of the future. The combination of efforts in both tissue engineering and regenerative medicine will likely be able to produce an artificial kidney in the near future.[55] With 3D printers becoming more established, it is likely that fabricated biomaterials will be produced, though difficulties could arise due to the heterogeneous makeup of an organ.[56] A further technique currently being studied in tissue regeneration is that of the bladder acellular matrix (BAM). This has the potential to improve surgical procedures that augment or substitute any or all of the bladder, which have previously led to complications such as stone formation, malignancy and bacteriuria.[57] The BAM, when seeded with stem cells, acts as a scaffold for tissue generation and engineering, potentially revolutionizing options for the creation of a neo-bladder and treating those with muscle invasive bladder cancer.[58] Great advancement in stem-cell therapy in urology is hoped for, but obstacles such as epigenetic changes, immune reactions and infection will need to be overcome.[59]

Likewise, nanotechnology will come to the forefront, aiding targeted therapies. Nanoparticles, no larger than 1000 nm, have been loaded with chemotherapeutic agents such as doxorubicin with high efficiency, sustaining the effect of chemotherapy in the body.[60] In fact, nanoparticles have been seen to enhance the chemotherapeutic action of apoptosis in prostate cancer cells.[61] Moreover, it has been demonstrated that nanoparticles are useful tools for gene therapy, as they are more efficient and safer

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Volume-15, October 2022
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than their viral vector counterparts in carrying genetic material into cells.[5,62]

With further regard to therapeutics it has also been noted that nanoparticle-directed laser therapy can result in directed tumour-specific ablation in the prostate, with the aid of ultrasound and MRI technology.[63] Although current studies have been limited in size, use of lasers has been seen to be clinically safe and efficacious.[64] However, more data will be required over the coming years before this practice becomes commonplace.

As well as in targeted medicines and therapies, nanotechnology will also be key in the future for much of urological equipment and imaging. For example, a ureteric stent built with nanofibres that degrade over time will help to reduce the rates of inflammation and infection compared with typical polyurethane stents.[65] In addition, the EnSeal™ nanotechnology system (Ethicon Endo-Surgery Inc., Cincinnati, OH, USA) has been seen to reduce the drawbacks of diathermy during laparoscopic surgery, through creating haemostasis at lower temperatures, acting to reduce damage to underlying structures.[66] Finally, nanotechnology has further enhanced MRI scanning by being able to extravasate into the interstitium of tumours, which can then be highlighted on subsequent imaging scans, increasing the sensitivity and specificity of carcinoma identification.[67] It is hoped that these advances will become common practice in later years.

With this large body of new technology just beyond the horizon, the training of the next generation of urologists is more important than ever. Though currently simulators form a core part of training,[68] thanks to improvements in computing power and interactivity, future simulators will implement augmented reality and virtual reality. This technology will be used in many ways, such as utilizing medical imaging to create 3D simulators for digital rectal examinations, or helping surgeons better understand procedures. Furthermore, technology will assist the development of surgeons aiding operations from afar in 'telesurgery'.[69] Finally, it is noteworthy that current advancements are being made in virtual consultations, as well as the recording of consultations, to further improve efficiency in the urological profession.[70–72]

CONCLUSION

It is clear that urological technology will advance in countless ways over the next two decades to create a personalized medicine through which each patient will receive targeted and specific therapy with minimal side effects. However, it is neglectful to not acknowledge that the advancements in genetics and targeted therapy may signal an end to many urological surgeries, such as cytoreductive nephrectomies, which are falling out of favour due to targeted therapies for kidney cancer.

Whilst the prehistoric urologist may have had to fend off a sabre-toothed tiger whilst treating his patient, the challenge to urological professionals of the future will be to utilize the technological advances of the world, to complement the growth in urological technology and better treat patients who require their services.

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