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Recent advances in the diagnosis, management and treatment of the most common urological disorders

Najnowsze osiągnięcia diagnostyczne i terapeutyczne najczęstszych chorób urologicznych

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Summary

The field of urology continues to evolve. There have been several major breakthroughs in the diagnosis and management of many urological diseases over last few decades. Just to mention the development of endourology, a subspecialty which not only does encompass visualisation of the upper and lower urinary tract but also modern management of diseases of the prostate. Other examples include ever growing field of laparoscopy or robotic urology itself to mention but the few.

Moreover, there has been a significant progress with regards to improvement of existing and development of new imaging modalities including magnetic resonance imaging which has advanced from being a standard anatomical imaging modality to one providing vital functional information about the cellularity of solid tissues (diffusion weighted imaging), perfusion parameters in neoplasms (dynamic contrast imaging), and relative concentration of intracellular metabolites (spectroscopy). Furthermore, recent advances in cancer genetics and genomics have changed our management paradigms in major urologic malignancies and have led to the development of new markers for detection, prognostication, and tailoring the most effective therapy in patients with cancers of the urinary tract.

This review discusses the recent advances in diagnosis and management of prostate, bladder, and renal cancers, as well as benign prostatic hyperplasia and urolithiasis.

Streszczenie

Urologia jest dynamicznie rozwijającą się dziedziną medycyny. W ostatnich dekadach dokonano przełomowych odkryć zarówno w zakresie diagnostyki, jak i leczenia chorób układu moczowo-płciowego. Jednym z nich jest rozwój endourologii, nowo wyłonionej poddyscypliny, która nie tylko pozwala na inspekcję od wewnątrz górnego i dolnego odcinka układu moczowego, ale również jest dedykowana do leczenia nowymi sposobami chorób stercza i pęcherza moczowego. Kolejnym przykładem jest powszechna dostępność chirurgii laparoskopowej, zarówno manualnej, jak i z asystą robota. Ponadto nadal rozwijane są dotychczasowe oraz tworzone nowe metody obrazowania chorób układu moczowego, jak na przykład rezonans magnetyczny, który ewoluował od bycia standardowym badaniem anatomicznym do badania, które dostarcza informacji czynnościowych dotyczących komórek tkanek litych (obrazy ważone dyfuzyjnie), informacji na temat przepływu krwi w tkankach (obrazowanie dynamiczne z wykorzystaniem środka kontrastowego) oraz pozwala na ocenę stężenia wybranych związków w badanym narządzie (spektroskopia rezonansu magnetycznego). Z kolei najnowsze osiągnięcia w zakresie genetyki i genomiki nowotworów w sposób istotny doprowadziły do zmian w postępowaniu w przypadkach nowotworów układu moczowego. Składa się na to m.in. odkrycie nowych markerów nowotworowych ułatwiających wykrywalność, prognozowanie oraz dobór właściwego leczenia chorych.

W opracowaniu przedstwiono bieżące osiągnięcia w zakresie diagnostyki oraz leczenia nowotworów gruczołu krokowego, pęcherza i nerek, łagodnego rozrostu stercza oraz kamicy dróg moczowych.

Konflikt interesów
Conflict of interest

Brak konfliktu interesów
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INTRODUCTION

The specialty of urology is under incessant change. Much of which has resulted from improved technology and advanced equipment. Newer techniques for better diagnosis and treatment of common urological diseases have enhanced early detection rates of urological cancers, reduced the operative trauma and optimized functional outcomes. Continuous improvements in management of malignancies, erectile dysfunction, benign prostatic hyperplasia (BPH), and renal stones have led to better quality of patients' life.

Several various alternatives have been recently investigated either to improve the diagnosis or to enhance the sensitivity of common diagnostic tools and techniques used in detection or treatment of the most popular urological diseases such as cancers, BPH and renal stones. In this review, we have looked at the latest developments within the diagnosis and management of several most common urological conditions.

DETECTION AND MONITORING OF UROLOGICAL CANCERS

Renal cell carcinoma

Renal cell carcinoma (RCC) is one of the most common cancers dealt with by urologists. This malignancy is characterized by a lack of early warning signs, diverse clinical manifestations, and resistance to radiation and chemotherapy (1). As with many other forms of cancer, patient outcome depends on the cancer stage and grade at diagnosis, its histological subtype, comorbidities and patient age. The 5-year overall survival for all types of RCC is 49%, whereas the 5-year survival rate after radical nephrectomy for stage I renal cell carcinoma, is approximately 94%, and for patients with stage IV disease is not higher than 20% (2, 3).

It is therefore of utmost importance to further improve renal cell cancer detection rates at an earlier stage of the disease.

In recent years there has been an increased interest in the prognostic role of the tumor markers, which most likely will better predict the clinical disease prognosis in future. The roles of neutrophil gelatinase-associated lipocalin, C-reactive proteins, plasmatic kisspeptin, beta-2-glickoprotein-1, alph-1-antitripsin and butyrylcholinesterase have been expanding (4-6). Additionally, latest data has suggested that nutritional screening is strongly associated with overall survival in patients treated with targeted agents for advanced renal cell carcinoma (7). Few recent studies have also shown that the metabolic profiles of glycolysis and pentose phosphate pathway in renal cell carcinoma, as well as, the pretreatment measurements of systemic inflammatory response, remain very important in overall patient's prognosis (8). More and more is known with regard to some genetic disorders, as well as other predisposing factors to renal cancer. The recent data has emphasized the role of piwi-interacting RNAs, FABP7 protein, MIR-141 expression, and, in particular, the specific miRNA role in clear cell renal carcinoma treatment. These all are being used in critical suppression of renal cell carcinoma proliferation and metastasis (9-11).

Our knowledge of predicting RCC outcomes is still under development, especially in terms of tumor size, grading, staging, lymph node involvement, and BMI in both cancer-specific and overall survival but it will inevitably grew with further advancements in analysis of cancer specific biomolecules and markers.

The role of imaging in the management of renal tumors has progressed in the past few years. The latest studies have shown that perinephric fat surface density (PnFSD) can significantly predict surgical complexity and perioperative outcomes of kidney surgery, especially robot-assisted partial nephrectomy (12). Moreover, new anatomical scoring systems for assessing technical complexity of kidney surgery have been introduced. Multiphasic computed tomography (CT), as well as the CT guided renal biopsies have become more useful than ever before in terms of diagnosis and management of small renal masses (13, 14). Targeted dual-modality imaging of renal cell carcinoma is still under investigation but preliminary results seem quite promising.

Prostate cancer

Role of MRI in prostate cancer detection

Prostate cancer (PCa) is the most common non-cutaneous cancer among males (15, 16). Although prostate cancer can be slow growing, the disease accounts for approximately 10% of cancer-related deaths in men (17). The diagnostic gold standard in prostate cancer (PCa) detection is based on abnormal digital rectal examination, an elevated serum PSA, and confirmatory transrectal ultrasound guided biopsy.

In recent years, multiparametric MRI (mpMRI) has emerged as an appealing tool facilitating significant prostate cancers pick-up rate (18). New data has suggested superiority of MRI-guided biopsy over non-targeted TRUS biopsy in detection of clinically significant disease (19). The addition of mpMRI to biopsy seems to have made an important step forward towards developing an ideal diagnostic test, with greater detection of more clinically significant lesions.

TREATMENT OF UROLOGICAL CANCERS

Expanding role of robotic surgery

Robot-assisted surgery is a technical solution using robotic systems in surgical procedures. It was developed to overcome limitations of minimally invasive procedures and to expand the capabilities of surgeons (20). This technique allows surgeons to enhance precision, flexibility and control, which are not otherwise possible with conventional techniques. It is safe, reproducible and offers several advantages to patients. With this method minimally invasive surgery is limitless. The benefits include: faster patient recov-

ery, shorter hospital stay, less pain and blood loss, smaller risk of complications including infections, less noticeable scars. With robotic procedure surgeons can perform complex operations that would have been otherwise difficult or impossible with conventional techniques. One of the major advances offered by robot-assisted surgery are remote control and unmanned procedures.

Robotic surgery is in many ways similar to laparoscopic surgery. It can be performed through smaller incisions compared to an open surgery. The most widely used clinical robotically-assisted surgical system includes a camera arm and mechanical arms with surgical instruments which are attached to them. Surgeon seats at a computer console, which gives him a high-definition, magnified 3D view of the surgical site. In this technique instead of directly moving the instruments, the surgeon uses one of two methods to control the whole system. It can be a direct telemanipulator or a computer control. Former is a remote manipulator that allows the surgeon to perform standard movements during surgery, while the robotic arms carry out those movements using end-effectors (e.g. cutting tools, graspers), and manipulators to perform the current surgery on the patient. In computer-controlled systems the surgeon uses a computer to control the robotic arms and its end-effectors but telemanipulators can also be used. Advantage of using this computerized method is that the surgeon does not have to be present. Performer can be anywhere in the world and this method leads to the possibility of remote surgery.

Compared with other minimally invasive surgery approaches and techniques, robotic surgery gives the surgeon a better control over the surgical movements and a better view of the surgical site. Moreover, surgeons no longer have to stand throughout the surgery and do not tire as quickly. Naturally occurring hand tremors are always filtered out by the robot's software. Finally, the surgical robot can be continuously used by rotating surgical teams.

In urology robot-assisted surgery has become very popular (21). As a consequence, a brand new interdisciplinary field called Urology Robotics or URobotics has emerged.

ROBOT-ASSISTED RENAL SURGERY

Kidney surgery is one of the most dynamically developing branches of robot-assisted surgery. This technique is used with high success rates in:

- robot-assisted pyeloplasty for ureteropelvic junction obstruction (both in pediatric and adult population),
- robotic radical nephrectomy (RRN),
- robotic partial nephrectomy (RPN, with ultrasound, TilePro multi-input display or fluorescence navigating),
- robotic radical nephroureterectomy,
- robotic ureter reimplantation (22-25).

Robot-assisted surgery of the upper urinary tract is becoming a routine method with excellent assistant. It is the translation of traditional surgery in a minimally invasive fashion offering more meticulous handling and miniaturisation of instruments. Reported data has proved feasibility of this technique, good oncological results and promising functional outcomes.

Robot-assisted laparoscopic prostatectomy

Robot-assisted laparoscopic prostatectomy (RALP) is a technique, which has gained widespread acceptance in the United States. Nowadays, about 84% of all radical prostatectomies in the U.S. are being done using robotic procedures. Similar trends have been observed in Europe, where RALP is becoming more available (26).

Robotic prostatectomy offers minimally invasive approach (27). This technique simplifies creation of a watertight vesicourethral anastomosis, which is a challenging step of radical prostatectomy (28). It allows surgeon to perform a proper dissection in the vesicoprostatic septum, better identification of the urethral tube, as well as bladder neck preservation (29). All of which have resulted with improved urinary continence.

In addition, RALP may lead to better potency rates in comparison to RRP (30). However, the oncological outcomes remain similar to those of RALP, LRP and RRP (31).

Current best evidence favors robotic prostatectomy over alternative approaches for selected outcomes (32). However, the aforementioned observations are based on a low level of evidence reflecting considerable uncertainty about its true benefits and harms.

IMMUNOTHERAPY IN UROLOGIC ONCOLOGY

After decades of research cancer immunotherapy has become an important new field of interest and subjects for clinical studies including urology. The results have raised hope that immunotherapy may provide new treatment options of prostate, bladder and renal cell carcinomas in future. Up until now we have had only general overview of this knowledge. Nowadays we are observing a significant growth in this field of urology. Future outlook of immunotherapy in the treatment of urologic malignancies seems promising.

Prostate cancer had the first approved vaccine treatment. One of the most notable therapeutic cancer vaccines is the Sipuleucel-T. Lots of clinical trails are underway and preliminary results are encouraging.

Additionally, some new immune modulatory agents may assist treatment in the challenging PCa cases. They can be administered either alone or in combination to patients with prostate cancer. Ipilimumab has been at the vanguard of this new immunotherapy approach. It targets the CTLA-4 checkpoint molecule on the activated immune cells (33).

Renal cell carcinoma is regarded as an immunologic tumor and studies exploring new targets in immunotherapy are currently underway. Novel agents for RCC treatment focusing on dendritic cell, checkpoint inhibi-

tion and peptide vaccination alone or in combination with established therapies will soon be introduced. The cytokines interleukin-2 (IL-2) and interferon-alpha cause a reduction in tumor mass in approximately 10-20% of patients and enable durable remissions in those subsets of patients. Moreover, adoptive cell therapy can help in renal cancer treatment. In this method immune cells are removed from the patient, then modified with genetic procedures or combined with some chemicals to enhance their activity. Next they are reintroduced into patient aiming to either trigger or strengthen the immunological anti-cancer response (34, 35).

Immunotherapy in bladder cancer is an extensive area of urology. Use of BCG has reduced the risk of bladder cancer recurrence and increased percentage of cases with a complete response after surgery. Ongoing immunotherapeutic clinical trials in patients with bladder cancer have been focusing on oncolytic virus therapy with tumor cells self-destruction, checkpoint inhibitors with anti-PD-L1(MPDL3280A) antibody and anti-PD-1 (Nivolumab) antibody to unleash or enhance pre-existing anti-cancer immune responses. There have also been several trials of vaccines especially with HS-410 and DEC-205-NY-ESO-1 fusion protein vaccine to induce immune response against tumor-specific or tumor-associated antigens. Recently some combined particles have been produced. There are combinations of cytokines and special antibodies, which recognize peptides on the surface of tumor cells (36-38).

NEW OPTIONS IN THE MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

Transurethral resection of the prostate (TURP) has been the gold standard treatment in men with lower urinary tract symptoms caused by benign prostatic enlargement, for more than 60 years. Its role, however, has been increasingly challenged by the development of minimally invasive techniques including laser procedures.

There are several types of lasers that are used in treatment of enlarged prostate, and include holium, thulium, or greenlight lasers (39-41). The most investigated laser procedure for BPH surgery is holium laser. It provides reliable histology and has comparable results to those of TURP or open surgery. Green light laser is relatively popular, safe, effective, easy to learn and can be used in anticoagulated patients. The disadvantage of the technique is that it does not provide tissue for histological examination, however.

In the 21st century, laser devices have challenged TURP. Therefore, TURP needs to be further optimized by reducing its rate of complications in order to remain still the gold standard and the mainstay of BPH surgical treatment.

ADVANCEMENTS IN THE MANAGEMENT OF UROLITHIASIS

Thanks to significant progress within technology interventional stone treatment patterns have considerably changed over the years. Nowadays, open stone surgery has been replaced by minimal-invasive techniques. Although conventional semi-rigid ureterorenoscopy (URS) and percutaneous nephrolithotomy (PCNL) seem to be the most common procedures, the frequencies of flexible ureterorenoscopy (FURS) and retrograde intrarenal surgery (RIRS) have been also increasing (42, 43).

The indications for FURS and RIRS have also expanded, though PCNL still remains the gold-standard treatment for large and/or complex renal stones. According to the newest data, there have been a high success rates in treating larger stones (2-3 cm) using a flexible ureterorenoscopy (43). FURS also appears to be a very safe technique, and can serve as an alternative to PCNL in selected patients with large renal calculi.

A new way of treatment, that also may be considered is a combination of procedures. Endoscopic Combined IntraRenal Surgery (ECIRS) is a fusion of PCNL and RIRS, that facilitates exploration of the entire renal cavity (44). Another combination of procedures is extracorporeal lithotripsy endoscopically controlled by ureterorenoscopy (45).

Innovative solution, which may revolutionise the future urology is robot-assisted flexible ureterorenoscopy (46). Its aim is to improve the FURS outcomes reducing side effects of both the surgeons and the endoscopes. It provides a suitable and safe platform, away from radiation source with significant improvement of ergonomics.

CONCLUSIONS

Urology is a rapidly changing and exciting area of medicine. Several new techniques and developments have been introduced in recent years aimed to improve the diagnosis and management of the most common urological conditions. Technological advances not only have facilitated better and earlier detection of urological diseases, but they also have provided more accurate, minimally invasive treatment tools with high efficacy, safety, and tolerability which have further allowed achieving better treatment outcomes. Further novel techniques and equipment will inevitably emerge and will be hopefully embraced and employed by urologists in their day to day clinical practice.

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