THE CANADIAN JOURNAL OF
UROLOGY™

Diagnosis, Treatment and Management of the Medical/Physical Sequelae of Prostate Cancer Therapy: The Primary Care Provider (Family Physician and Nurse Practitioner)-Specialist: Partnership

Indexed in
***Index Medicus*/**
MEDLINE
and
***Current Contents*/**
Clinical Medicine

Volume 27
Supplement 1
February 2020

ISSN 1195-9479

THE CANADIAN JOURNAL OF
UROLOGY™

Indexed in
Index Medicus/
MEDLINE and
Current Contents/
Clinical Medicine

Volume 27
Supplement 1
February 2020

 The Canadian Journal of Urology is published six times a year by CJU Communications Inc., located at 2330 Ward St., Suite 604, St. Laurent, QC, H4M 2V6 Canada. Canadian Publication. ISSN 1195-9479. Publications Mail Agreement Number 40028816. Postage paid at Saint Laurent, Quebec. Printed in Canada. Printed on acid-free paper. Visit us at **www.canjurol.com**.

George Georgieff	Lena Georgieff	Francine Iwersen	Advertising Sales: Mtl.
Publisher	Editorial Coordinator	Graphics	Tel.: (514) 744-1184

THE CANADIAN JOURNAL OF
UROLOGY™

Indexed in Index Medicus/MEDLINE and Current Contents/Clinical Medicine

Contents

Volume 27, Supplement 1, February 2020

CONTRIBUTORS

Jack Barkin, MD / Editor
Department of Surgery
University of Toronto
Toronto, Ontario

Dean S. Elterman, MD
Division of Urology
University of Toronto
Toronto, Ontario

Kyle W. Law, BSc
Faculty of Medicine
McGill University
Montreal, Quebec

Diana E. Magee, MD
Division of Urology
University of Toronto
Toronto, Ontario

David-Dan Nguyen, MPH(c)
Faculty of Medicine
McGill University
Montreal, Quebec

Seyed Hossein Saadat, MD
Division of Urology
University of Toronto
Toronto, Ontario

Valentin Shabataev, MD
Division of Urology
University of Toronto
Toronto, Ontario

Rajiv Singal, MD
Division of Urology
University of Toronto
Toronto, Ontario

Kevin C. Zorn, MD
Division of Urology
University of Montreal Hospital Center (CHUM)
Montreal, Quebec

EDITORIAL

The Primary Care Provider (Family Physician and Nurse Practitioner)-Specialist: Partnership

Over the last number of years, I have written and/or edited numerous supplements for *The Canadian Journal of Urology* (CJU) on the theme of "update or guidebook" in the management of urologic conditions by the family care physician (FP). It had become evident to us that patients with so many urologic conditions such as urinary tract infections, benign prostatic obstruction, overactive bladder, erectile dysfunction, hypogonadism and elevated prostatic-specific antigen (PSA) to name just a few, first present to the primary care provider (PCP) for diagnosis and management.

In this past decade, I have had the privilege of addressing, either directly or through the CJU, literally tens of thousands of PCP's on these topics.

The feedback has always been very gratifying as the PCP's express their appreciation for providing them the tools and knowledge to diagnose and initiate evidence-based therapy for some of these conditions, as well as been given the understanding when to escalate to the Urologist.

Prostate Cancer, the number one diagnosed cancer in man and the second or third commonest killing cancer in North American men, has always been confusing and scary for the PCP. Confusing, because they have been told that it is a benign disease for which previous task forces both in the USA and Canada have discouraged PSA screening and also scary because they have all had patients with "BAD" prostate cancer that was missed or patients diagnosed with aggressive prostate cancer that, if not treated , would have died. It is also difficult, because as with every type of cancer, there is always a chance that the curative treatment whether surgical or radiation, may cause certain physical/lifestyle side effects and the medical therapy may also exacerbate or accelerate other medical conditions/co-morbidities.

In this latest supplement we have addressed the issues surrounding prostate cancer. It is obvious that the PCP plays a critical role at all levels in patient management. I am never surprised when a patient that has been referred to me by his PCP for diagnosis and ultimately confirmation of his prostate cancer, having discussed the options and recommendations, will in about 80% of the cases then inform me that he is going back to his PCP to discuss the problem and make a joint decision on management.

This supplement is being written to provide the 2020 recommendations and insights into the diagnosis and management of prostate cancer and the potential sequelae of management, always with the role of the PCP being defined.

In our first article: on the Diagnosis of Prostate Cancer: by Zorn, Barkin et al, we review the task force recommendations and discuss why they may have been incorrect. We then give an extensive update as to the utility of PSA and its variants by the PCP, to help determine which patients should have a biopsy or the use of additional new biomarkers or other diagnostic tests to support the suspicion of clinically significant prostate cancer, before doing the biopsy.[1]

In the next article by Singal et al, Androgen Deprivation Therapy(ADT): and all of its components, we again present the thought process as to in whom and why to use ADT, being aware of its potential risks and benefits. There are certain potential side effects and interactions that the urologist and the PCP must be aware of, address and manage in prostate cancer patients using hormonal blockade.[2]

Finally, in the third article by Elterman et al: Management of the E.D. and/or Incontinence Secondary to Prostate Cancer Management. The authors review the medical and interventional management of these potential side effects after either surgery or radiation for the eradication of prostate cancer in your patients.[3]

We hope that this supplement will identify and confirm the respective roles and partnership between the PCP and Urologist in the diagnosis of prostate cancer and the sequelae of its primary treatment and medical management.

Dr. Jack Barkin
Clinical Professor
Department of Surgery,
University of Toronto
Toronto, Ontario, Canada
Executive Deputy Editor

References

1. Law KW, Nguyen D-D, Barkin J, Zorn KC. Diagnosis of prostate cancer: the implications and proper utilization of PSA and its variants; indications and use of MRI and biomarkers. *Can J Urol* 2020;27(Suppl 1):3-10.
2. Magee DE, Singal RK. Androgen deprivation therapy: indications, methods of utilization, side effects and their management. *Can J Urol* 2020;27(Suppl 1):11-16.
3. Shabataev V, Saadat SH, Elterman DS. Management of erectile dysfunction and LUTS/incontinence: the two most common long term side effects of prostate cancer treatment. *Can J Urol* 2020;27(Suppl 1):17-24.

Diagnosis of prostate cancer: the implications and proper utilization of PSA and its variants; indications and use of MRI and biomarkers

Kyle W. Law, BSc,[1] David-Dan Nguyen, MPH(c),[1] Jack Barkin, MD,[2] Kevin C. Zorn, MD[3]

[1]Faculty of Medicine, McGill University, Montreal, Quebec, Canada
[2]Department of Surgery, University of Toronto, Toronto, Ontario, Canada
[3]Division of Urology, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada

LAW KW, NGUYEN D-D, BARKIN J, ZORN KC. Diagnosis of prostate cancer: the implications and proper utilization of PSA and its variants; indications and use of MRI and biomarkers. *Can J Urol* 2020;27(Suppl 1):3-10.

Prostate cancer screening remains highly controversial in medicine. The College of Family Physicians of Canada currently endorses positions that recommend against prostate-specific antigen (PSA) screening in men of all ages, while the Canadian Urological Association recommends shared and informed decision making for PSA screening in men 50-70 years old. Unfortunately, these opposing stances have left Family Physicians responsible for interpreting the appropriate course of action for their patients. Recent studies demonstrating an increase in incidence of metastatic prostate cancer have led to our support of the Canadian Urological Association recommendations.

In an attempt to facilitate initial patient investigation, this article aims to outline current prostate cancer screening recommendations, as well as the various screening modalities available. The utility of PSA-based tests, serum and non-serum biomarkers, and multiparametric magnetic resonance imaging is discussed and evaluated.

Key Words: biomarkers, prostate cancer screening, recommendations

Prostate cancer screening

The goal of prostate cancer screening is the early detection of clinically significant prostate cancer as opposed to low-risk disease that would otherwise have no clinical impact. Despite all the advances in screening technology, prostate cancer screening remains one of the most controversial topics in urology. In a Cochrane review published in 2013, systematic prostate-specific antigen (PSA) screening resulted in higher diagnoses of prostate cancer but yielded no benefits for overall survival (OS; RR: 1.00; 95% CI, 0.96-1.03) or cancer-specific survival (CSS; RR: 1.00; 95% CI, 0.86-1.17).[1,2]

Address correspondence to Dr. Kevin C. Zorn, University of Montreal Hospital Center (CHUM), 235 Rene Levesque Est, Suite 301, Montréal, QC H2X 1N8 Canada

Moreover, screening-associated overdiagnosis and overtreatment, with consequences such as decreased patient quality of life and economic burden on the system, have led to guidelines discouraging the use of systematic PSA screening in Europe and the United States.[3] However, based on the conclusions of three randomized control trials (the Prostate, Lung, Colon, and Ovarian screening trial (PLCO),[4] the European Randomized Study of Screen for Prostate Cancer (ERSPC; 21% RR reduction in prostate cancer mortality),[5] and the Goteborg randomized trial of PSA screening (42% RR reduction in prostate cancer mortality),[6] the Canadian Urological Association (CUA) concluded that PSA screening appears to reduce prostate cancer mortality, supporting their suggestion to have a discussion about screening in men between the ages of 50-70 who were interested in

pursuing examinations.[7] Despite the recommendation to offer PSA screening, the CUA recognizes the risk of overdiagnosis and overtreatment, especially since up to 67% of men diagnosed with prostate cancer will be identified as having clinically insignificant disease (no impact on morbidity or mortality).[7] Therefore, there is a large emphasis on the importance of detailed investigation prior to proceeding with prostate biopsy. Investigations including PSA measurements and its variants, emerging serum and non-serum biomarkers, and new prostate imaging techniques will help guide clinical decision-making, with the aim to reduce unnecessary prostate biopsies.

Informed decision-making

It is necessary to hold a thorough discussion regarding the pursuit of prostate cancer screening with patients meeting screening recommendation criteria as per CUA recommendations highlighted below.[7] It is essential to outline both the benefits and risks associated with prostate cancer screening while taking into account the personal values and interests of the patient. Important risks of prostate cancer screening include potential harm from prostate biopsy (e.g. bleeding, infection or sepsis) and psychological stress endured by the diagnosis of prostate cancer, specifically in cases where men may not have clinically significant disease. Consequently, the CUA stresses that prostate screening is to remain an individualized process. Informed men between the ages of 50-70 requesting prostate cancer screening should be given a digital rectum examination (DRE) and PSA testing.

The College of Family Physicians of Canada and CUA stances on prostate cancer screening

In 2012, the United States Preventative Services Task Force (USPSTF), a panel that did not include urologists or cancer specialists, recommended against PSA screening on the basis that the small decrease in mortality provided by screening does not outweigh the harms of screening and overdiagnosis.[8] Following suit in 2014, the Canadian Task Force on Preventative Health Care (CTFPHC) published a strong recommendation against PSA screening in men less than 55 years of age, and men greater than 70 years of age. In addition, they recommended against PSA screening for men between the ages of 55-69 years.[9] Subsequently, the College of Family Physicians of Canada (CFPC) endorsed the statements of the CTFPHC. This opinion opposed statements made by both the CUA,[7] the American Society of Clinical Oncology (ASCO),[10] and other societies,[3,11] which recommended shared decision making for PSA screening in men aged 50-70 and 55-69, respectively. Unfortunately, this has left Family Physicians hesitant because of two contradictory positions on PSA screening without clear direction.

Following the recommendations of the USPSTF against PSA screening, studies were employed to determine long term outcomes. In the 2 years following USPSTF recommendations, there was a significant decrease in PSA screening tests administered and biopsy volume decreased by 31%. It was also reported that patients were more likely to be diagnosed with high-risk disease/metastatic disease and less likely to be diagnosed with intermediate-risk/curable disease.[12] It is important to note that these conclusions were drawn from registry-based studies, which may have overemphasized the potential downside of the recommendation against use of PSA testing without considerations for the pitfalls such as overtreatment. Nonetheless, analysis of the USPSTF recommendations found major flaws in the trials on which the recommendations were based. In depth analysis revealed a high rate of non-protocol PSA measurements in the control group, which may have rendered the results of the trial inconclusive. In addition, authors found that the trials had a median follow up of approximately 10 years, which was believed to be inadequate for slowly progressing prostate cancer. Some of the other studies used when performed in pure – unscreened or contaminated populations, show increased survival and a smaller number of patients needed to screen to cure one individual.[13] Furthermore, an epidemiological study in 2018 found that the incidence of metastatic prostate cancer in the United States was increasing by 2.74%/yr in 2012 following the statements of the USPSTF, compared to a previous decline in metastatic prostate cancer incidence by 1.45%/yr in 2007.[14] Another imperative aspect to consider was that one of the major rationales behind the recommendations of the USPSTF and the CTFPHC was the overtreatment of low-risk prostate cancer and its associated morbidity. In 2009, conservative management was utilized in 6.7% of cases of low-risk prostate cancer in the United States. Between 2010 and 2013, conservative management for men with low-risk PCa, rose sharply to 40.4% of cases [15]. An increased uptake of active surveillance as a treatment modality demonstrated that urologists are being more responsible with low-risk and intermediate-risk patients; thus, more responsible with PSA screening results. This, as well as a concerning trend of increased high-risk disease at presentation, has led to our strong support of CUA guidelines on PSA screening.

PSA screening recommendations, Figure 1

For men electing to undergo PSA screening, the CUA recommends that PSA measurements begin at age 50 for most men, and at age 45 for men with an increased risk of developing prostate cancer.[7] Primary risk factors for prostate cancer that influence PSA screening practices include age (> 50 yr) and family history of prostate cancer. In men aged < 50 years, history of prostate cancer in a first-degree or second degree relative conferred a five-fold and two-fold risk of receiving a prostate cancer diagnosis, respectively, and therefore screening can be offered at 45 years.[16] Men with African ethnicity origin show higher incidences of prostate cancer and generally have a more lethal course of disease and therefore can be offered screening at 45 years.[17] Interestingly, the risk of developing metastatic prostate cancer within 15 years in men less than 45 years was very low, including men who tested in top PSA percentiles. Therefore, PSA screening for men under 45 is unlikely to provide any benefit.[16]

Since 2017, the CUA guidelines suggest that the interval between PSA testing should be based upon initial PSA measurements. For men with PSA < 1 ng/mL, PSA testing should be repeated every 4 years, as the risk of developing metastatic disease within 15 years for a man of any age with a PSA < 1 ng/mL is very low.[7] Baseline PSA levels above 1 ng/mL are at increased risk of clinically significant prostate cancer and/or prostate cancer metastasis several decades later[18,19] and therefore the CUA recommends offering repeat PSA screening every 2 years. For PSA levels > 3 ng/mL, the CUA have not specified an optimal testing interval, but recommend more frequent PSA testing and further investigations with adjunctive testing strategies (PSA velocity, PSA density and percent free PSA).

As per CUA recommendations, screening discontinuation should be based on current PSA levels and life expectancy. For asymptomatic men at age 60 with PSA level < 1 ng/mL, the risk of developing metastatic prostate cancer is low and therefore standard screening is no longer justified.[7] Similarly, the CUA recommends discontinuing PSA screening in asymptomatic men at age 70 as the ERSPC trial concluded that screening at > 70 yr did not reduce prostate cancer mortality,[5] though PSA testing can be continued in those who are interested. In addition, the CUA recommends discontinuing PSA screening in men with a life expectancy less than 10 years. For men with a high risk of mortality from external factors, PSA screening is unlikely to provide any benefit and therefore should not be offered or can be discontinued.[20] Ultimately, the health care provider should take into account the patient's current age, general health status, and values/interests when deciding to offer PSA screening.

PSA investigations

Most prostate cancers are located in the peripheral zone of the prostate and pathologies may be detected by DRE when volume > 0.2 mL. Serum PSA is an organ-specific but not cancer-specific serum marker, and therefore can be elevated in non-malignant prostate pathologies such as benign prostatic hyperplasia (BPH), and prostatitis. Moreover, men may present with prostate cancer despite having low serum PSA.[21] Clinically, prostate cancer is suspected on the basis of abnormal DRE and/or elevated PSA levels. In asymptomatic men with total serum PSA levels between 2-10 ng/mL, further risk investigation including prostate volume assessment to calculate PSA density, PSA kinetics, and free/total PSA ratio are recommended prior to proceeding with prostate biopsy.[3] Initial prostate investigations begin with serum PSA levels, its variants, and the DRE and should be used in accordance to guide clinical decision-making.

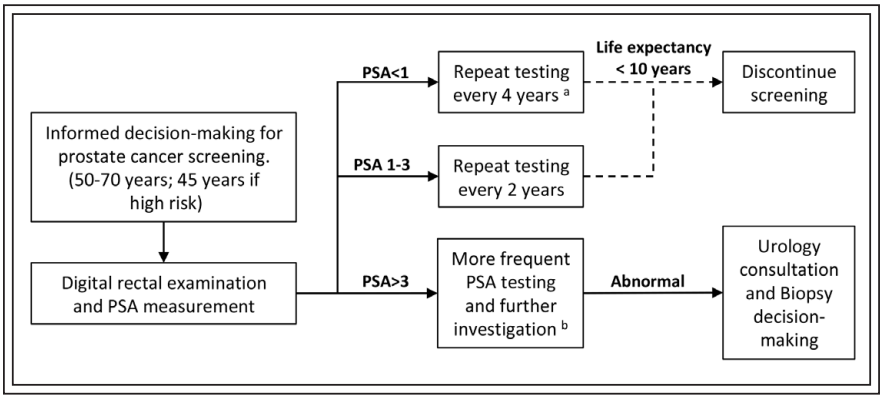

Figure 1. Prostate cancer screening decision-making algorithm. **a)** Discontinue screening in asymptomatic men if age > 60 and PSA < 1 ng/mL. **b)** e.g., Free/total PSA, serum and non-serum biomarker tests, etc. PSA = prostate-specific antigen.

PSA density

PSA density (PSAD) is the serum PSA divided by transrectal ultrasound (TRUS)-determined prostate volume. Prostate volume can also be assessed by transabdominal ultrasound, CT imaging or MRI. Some studies have shown that a PSAD threshold of < 0.15 ng/mL/cm^3 in a highly selected population with limited cancer on biopsy distinguished men with insignificant tumors,[22] whereas other studies failed to validate these findings.[7] The CUA therefore discourages the use of PSAD alone but instead suggests that it should be used as an adjuvant to absolute PSA levels in order to contribute to clinical decision-making.

PSA kinetics

PSA velocity (PSAV), the absolute annual increase in serum PSA (ng/mL/year), and PSA doubling time (PSADT) are both measures of how serum PSA is changing over time. Indeed, substantial increases in PSA over time is concerning and warrants further investigations. Some studies have shown that a PSAV greater than 0.75 ng/mL/year indicate increased risk of prostate cancer, and that PSAV may potentially be used as a prognostic tool for prostate cancer treatment, while other studies have shown conflicting evidence.[7] Additionally, PSA kinetics are limited as a diagnostic tool due to variations in PSA measurement intervals. As such, the CUA discourages the use of PSA kinetics alone; it should be used to provide additional information about prostate cancer risk.

Free/total PSA ratio

The ratio of free to total PSA is useful for men with a total PSA of 4-10 ng/mL and a negative DRE. Studies preceding the use of biomarkers and MRI to determine prostate cancer risk (discussed below) demonstrated that prostate cancer was detected by biopsy in 56% of men with a free-to-total ratio less than 0.1 ng/mL, but in only 8% of men with a free-to-total ratio greater than 0.25 ng/mL.[23] In other words, a higher free-to-total ratio was found to confer a lower risk of harboring prostate cancer. It is important to note that the free-to-total PSA ratio has no clinical use if serum PSA is > 10 ng/mL or during follow up for known prostate cancer.[3] Similar to serum PSA levels, the free/total PSA ratio can fluctuate, thus repeated testing is necessary before clinical decision-making. As such, the CUA does not recommend using the free/total PSA ratio alone for clinical decision-making, but it is an effective tool for men with elevated serum PSA levels in determining if prostate biopsy is necessary.

Prostate cancer related biomarkers

In order to avoid unnecessary biopsies, the European Association of Urology (EAU) recommend that all asymptomatic men with PSA between 2-10 ng/mL receive further risk assessment in addition to PSA measurements and its variants. Further investigation includes either a validated prostate cancer risk calculator, or additional biomarker testing (4Kscore, PHI test, or PCA3 test).[3] The CUA recognizes that in men with moderately elevated PSA (2-10 ng/mL), biomarker tests such as the 4Kscore, PHI, PCA3, SelectMDx, and ExoDx are emerging as very effective tools in predicting clinically significant prostate cancer when compared to PSA measurements alone. At the current moment, many of these tests are not publicly funded in Canada,[7] nonetheless, their use is increasing in the urology community due to their effectiveness and potential to reduce unnecessary prostate biopsies from occurring.

Serum liquid Testing; 4Kscore

Aside from direct PSA related measurements, additional biomarkers measured in patients' blood serum may be used to estimate prostate cancer risk. The four-kallikrein panel (4Kscore) is a test that measures free, total, and intact PSA and human kallikrein-like peptidase 2. The test combines these results with age, DRE results, and prior biopsy status to estimate patient risk of harboring "clinically significant " cancer meaning Gleason 7 or greater disease.[7] Although popular since it was one of the first biomarker tests available, the 4Kscore relies heavily on PSA parameters, presenting a large problem for the select population of men harboring clinically significant disease without elevated PSA levels.[21] Additionally, the Centers for Medicare and Medicaid Services (USA) will not cover 4Kscore testing under Medicaid as they found an absence of clinical utility and had significant issues with validating initial findings,[24] therefore this test is not recommended.

Serum liquid testing; Prostate Health Index (PHI)

PHI is a validated test that measures free and total PSA, and the (-2)pro-PSA isoform to similarly estimate the risk of harboring Gleason 7 or greater disease. The PHI test is a commercially available test that outperformed free/total PSA in distinguishing clinically significant disease, specifically in men with PSA between 2-10 ng/mL.[25] The PHI and 4Kscore tests both performed similarly in predicting high-risk prostate cancer in men in a direct comparison between the two.[26] Since the clinical effectiveness of the 4Kscore was not validated during further investigations, the PHI test should also be used with caution.

Serum liquid testing; NK Vue

Natural killer (NK) cells are involved in tumor cell immunosurveillance and decreased NK cell activity (NKA) has been associated with prostate cancer. The NK Vue test involves an in vitro assay using 1 mL of the patient's blood. In a small pilot study, NKA was measured prior to prostate biopsy using the NK Vue blood test. The study concluded a positive predictive value of 86% and a negative predictive value of 69% using a cut off of 200 pg/mL for NKA and that low NKA values were more likely to be associated with a positive prostate biopsy.[27] NK Vue is an emerging, commercially available test that is relatively inexpensive and may provide helpful information in predicting high-grade prostate cancer.

Non-serum liquid testing: Prostate Cancer Antigen 3 (PCA3)

PCA3 is a prostate-specific non-coding mRNA biomarker that can be measured in urine following prostatic massage during DRE. Progensa, the commercially available PCA3 test, was found to be superior to total and free/total PSA for the detection of prostate cancer in men with elevated PSA.[28,29] The indication for PCA3 testing is in men with a previous negative biopsy result to determine if a repeat biopsy is necessary. A large prospective study demonstrated that men with a history of negative prostate biopsy who scored lower than 25 on the Progensa test were approximately 5 times less likely to have a positive repeat biopsy when compared to men who scored 25 or greater.[30] The PCA3 test has not been validated for biopsy-naïve patients i.e. patients being treated with active surveillance.

SelectMDx

SelectMDx utilizes clinical findings (PSAD, DRE, PSA, age, history of biopsy, and family history of prostate cancer) and RNA levels of *HOXC6* and *DLX1* genes measured in post-DRE urine, to predict Gleason ≥ 7 disease on biopsy. Unlike the 4Kscore, SelectMDx relies less on PSA findings and incorporates unrelated RNA profiles to assess prostate cancer risk, not limiting its effectiveness in the select men harboring clinically significant disease that present with normal PSA profiles. In a prospective study of 519 patients scheduled for biopsy, the SelectMDx algorithm achieved an AUC of 0.90 (95% CI, 0.85-0.95) for the detection of high-grade prostate cancer.[31] The study concluded that the algorithm resulted in better prostate cancer risk stratification when compared to current clinical practices. Overall, Select MDx is a promising algorithm that incorporates clinical findings and biomarkers to predict high-grade prostate cancer, an additional tool that could reduce the number of unnecessary prostate biopsies.

ExoDx Prostate Intelliscore (EPI)

EPI combines clinical findings (age, PSA, race, family history of prostate cancer) with expression of PCA3 and ERG found within patients' urine to predict Gleason ≥ 7 disease on biopsy. One advantage of the EPI test is that it does not require post-DRE urine, which may benefit patients undergoing testing.[32] The test was validated in 1064 patients scheduled for biopsy (≥ 50 years, prostate cancer free, PSA 2-20 ng/mL).[33] When compared with clinical findings alone, the addition of the PCA3 and ERG biomarkers in the EPI test was associated with improved discrimination between Gleason 7 or greater and Gleason 6 and benign disease (AUC = 0.73, 95% CI: 0.68-0.77 in EPI versus AUC = 0.63, 95% CI: 0.58-0.68 in clinical findings alone). The authors also concluded that if the EPI test had determined biopsy decisions in their study, 27% of biopsies (138 out of 519) would have been avoided, missing only 5% of patients with Gleason 7 (4+3) disease. EPI is another promising test available that may reduce the number of unnecessary prostate biopsies by better discriminating clinically significant disease.

Serum (4Kscore, PHI) and non-serum (PCA3, SelectMDx, EPI) biomarkers for prostate cancer detection have become a popular tool in distinguishing between clinically significant and non-significant disease. In addition to the patients' clinical presentation and findings, these biomarker tests are more effective than PSA measurements alone in predicting high-grade disease. These available tools can be used to help guide clinical decision-making, potentially reducing the number of unnecessary biopsies performed, Figure 2.

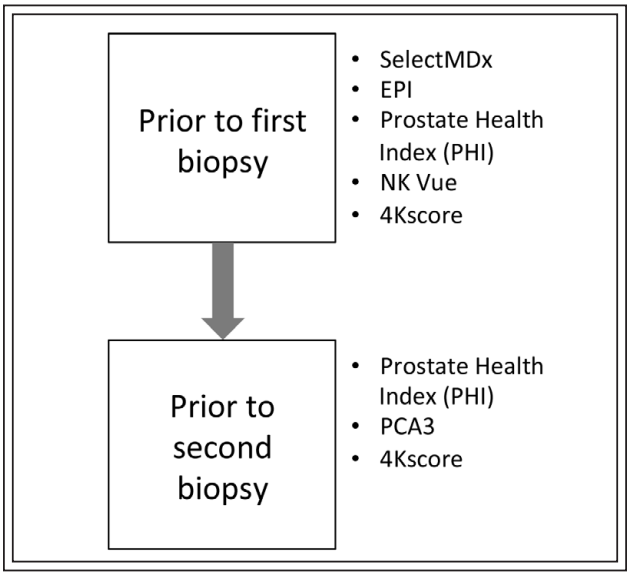

Figure 2. Prostate cancer biomarker tests and the decision points in which they have been validated.

Prostate risk calculators

The use of nomograms to assess the risk of clinically significant prostate cancer before biopsy are attractive as they are easy to use, available online and supplement the use of PSA alone.[7] Among the most widely used calculators, the PCPT[34] and ERSPC[35] prostate cancer risk calculators are the most popular. These and similar calculators can be used to assess the risk of harboring clinically significant prostate cancer prior to biopsy, though a systematic review and meta-analysis demonstrated that only few of the available calculators improved the predictive accuracy of PSA testing to detect clinically significant prostate cancer (among the few were the PCPT and ERSPC risk calculators).[31]

Multiparametric magnetic resonance imaging (mpMRI) of the prostate gland

mpMRI combines anatomical and functional MR sequences to investigate any lesions in the prostate. The combination of sequences (dynamic contrast enhancement, T2W-weighted imaging and diffusion weighted imaging) allows for the interpretation of any suspicious lesions and may help guide prostate biopsy.[36] Dynamic contrast-enhanced images utilize IV contrast to assess the vascularity of the prostate. Prostate cancer tumors can be localized due to increased blood flow on imaging because of neovascularization that often accompanies the tumor's growth. T2W-weighted imaging reflects local tissue water and may be used to delineate the anatomy of the prostate i.e. the peripheral and transition zone. Diffusion weighted imaging analyzes the motion of water molecules. Due to the relatively increased density of tissue found in cancer tissue, there is less motion detected on imaging. This can help localize prostate cancer lesions. These sequences can combine digitally to generate a 3D representation of the lesion's location. Subsequently, the image can be used to help guide prostate biopsy. If there is an abnormal finding, ultrasound of the prostate is digitally mapped with the MRI image in real time using a fusion software, allowing the operator to target specific abnormal areas during the biopsy procedure. The CUA does not recommend mpMRI followed by targeted biopsy in biopsy-naïve men with an increased risk of prostate cancer (elevated PSA/risk calculator), as Cancer Care Ontario released a systematic review indicating that the diagnostic abilities of mpMRI were poor to moderate in a biopsy-naïve setting.[37] Thus, systematic TRUS-guided biopsy (with no prior imaging) remains the gold standard for biopsy-naïve men. However, in men with a prior negative TRUS-guided biopsy who show signs of increased prostate cancer risk (increasing PSA levels or increasing abnormalities in DRE), mpMRI followed by targeted biopsy, may prove helpful in diagnosing more clinically significant prostate cancer, and fewer low-risk cancers when compared to patients with a repeat TRUS-guided biopsy.[7,38]

PIRADs scoring system

The reporting of prostate mpMRI examination is expressed using the Prostate Imaging – Reporting and Data System (PIRADS) score. Using parameters such as T2-weighted, diffusion weighted, and dynamic contrast enhanced imaging of the mpMRI, a sum is calculated from values assigned to each variable and is interpreted according to the PI-RADS classification which ranges from 1 to 5, with 1 being most probably benign and 5 most probably malignant.[39,40] In a phase II retrospective clinical trial, it was concluded that the global consensus PIRADS showed high sensitivity and positive predicted value, reduced surgery for indolent prostate cancer [41], and improved the diagnosis of clinically significant prostate cancer when compared to standard diagnostic tools such as transrectal ultrasound biopsies.

Prostate biopsy

Ultrasound-guided biopsy

In ultrasound-guided biopsy, the standard biopsy approach in the context of prostate cancer, the operator uses ultrasound during the procedure to guide their needle. The most common approach for prostate sampling is transrectal ultrasound-guided biopsy (TRUS), while a transperineal approach may be implemented for men who cannot undergo a transrectal procedure e.g. anal stenosis.[42] TRUS is performed in an office setting with local anesthesia. Both the ultrasound probe and biopsy needle are inserted through the rectum and the prostate is sampled extensively in a systematic, but blind fashion (the samples taken are "randomly"). Though some studies suggest that prostate volume should be taken into account when performing a biopsy,[43] a standard 12 core biopsy approach is often implemented, sampling from the apex, base, mid-prostate and lateral aspects of the prostate on each side. In addition to systematic sampling, specific guided sampling of abnormal areas (e.g. hypoechoic regions, DRE, MRI) may be carried out.

Gleason score and new ISUP

The Gleason score system is utilized by pathologists to grade prostate cancer. When analyzing a prostate biopsy, there is often variation in regard to the grade

TABLE 1. **Interpretation of ISUP grade groups**

ISUP grade group	Gleason score equivalent	Risk group
Grade group 1	Gleason score < 6	Low
Grade group 2	Gleason score 7 (3+4)	Intermediate favorable
Grade group 3	Gleason score 7 (4+3)	Intermediate unfavorable
Grade group 4	Gleason score 8	High
Grade group 5	Gleason score 9-10	High

of cancer present between different areas of a single sample. As such, two grades are assigned to the two areas that comprise the majority of the cancer within the sample, grade 1 having the best prognosis, grade 5 having worst. The two grades are added to yield the Gleason score. When reporting a Gleason score, the grade of the largest and most abnormal area of the sample is reported first. For example, a biopsy sample scored with Gleason 7 (4+3) refers to a lesion that is primarily comprised of grade 4 findings, while fewer areas of the lesion are grade 3.[44,45]

In 2015, the International Society of Urological Pathologists (ISUP) released a revised and simplified prostate cancer grading system called the ISUP Grade Groups. There are 5 grades, 1 through 5. These grades groups are based on the traditional Gleason score and are associated with prostate cancer risk groups, Table 1.[46,47] Both scoring systems are used in practice.

Conclusion

As Family Physicians, individualized discussions regarding the pursuit of PSA screening should be held with all patients meeting CUA prostate cancer screening guidelines. Asymptomatic men with an abnormal DRE, and men with PSA > 3 ng/mL, as well as abnormal serum/non-serum biomarker test results should receive a referral to a specialist. In addition, symptomatic men showing signs of lower urinary tract symptoms (frequency, urgency, incontinence etc.) should also receive a referral to a specialist. Although it is recommended by national CUA guidelines for men 50-70 years old, PSA screening remains a controversial decision. While former kinetics and PSA-based calculations have helped in the guidance of patient counseling for prostate biopsy, the emergence of biomarkers (SelectMDx, etc.) and mpMRI continue to grow as more specific tools for accurate patient counseling prior to prostate biopsy. With the well-known overdiagnosis and overtreatment of Gleason 6 non-significant prostate cancer, these non-invasive tools are growing in the urological community to assist in improved patient care and counseling. We hope that this article will empower Family Physicians to properly utilize prostate cancer screening modalities; allowing for appropriate escalation of patients to specialists for further investigation and management. □

References

1. Ilic D, Neuberger M, Djulbegovic M, Dahm P. Screening for prostate cancer. *Cochrane Database Syst* Rev 2013;1(CD004720).
2. Hayes J, Barry M. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. *JAMA* 2014;311(11):1143-1149.
3. Mottet N, Bellmunt J, Bolla M et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71(4):618-629.
4. Andriole GL, Crawford ED, Grubb RL et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360(13):1310-1319.
5. Schröder FH, Hugosson J, Roobol MJ et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360(13):1320-1328.
6. Hugosson J, Carlsson S, Aus G et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010;11(8):725-732.
7. Rendon RA, Mason RJ, Marzouk K et al. Canadian Urological Association recommendations on prostate cancer screening and early diagnosis. *Can Urol Assoc J* 2017;11(10):298-309.
8. Moyer VA, U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2012;157(2):120.
9. Bell N, Gorber SC, Shane A et al. Recommendations on screening for prostate cancer with the prostate-specific antigen test. *Can Med Assoc J* 2014;186(16):1225-1234.
10. Bekelman JE, Rumble RB, Chen RC et al. Clinically localized prostate cancer: ASCO Clinical Practice Guideline Endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology Guideline. *J Clin Oncol* 2018:JCO1800606.
11. Carter HB, Albertsen PC, Barry MJ et al. Early detection of prostate cancer: AUA Guideline. *J Urol* 2013;190(2):419-426.
12. Eapen RS, Herlemann A, Washington SL, Cooperberg MR. Impact of the United States Preventive Services Task Force 'D' recommendation on prostate cancer screening and staging. *Curr Opin Urol* 2017;27(3):205-209.

13. Catalona WJ, D'Amico AV., Fitzgibbons WF et al. What the U.S. Preventive Services Task Force missed in its prostate cancer screening recommendation. *Ann Intern Med* 2012;157(2):137.
14. Kelly SP, Anderson WF, Rosenberg PS, Cook MB. Past, current, and future incidence rates and burden of metastatic prostate cancer in the United States. *Eur Urol Focus* 2018;4(1):121-127.
15. Murphy DG, Loeb S. Growth of AS in the USA signals reduction in overtreatment. *Nat Rev Urol* 2015;12(11):604-605.
16. Albright F, Stephenson RA, Agarwal N et al. Prostate cancer risk prediction based on complete prostate cancer family history. *Prostate* 2015;75(4):390-398.
17. Tan DSW, Mok TSK, Rebbeck TR. Cancer genomics: diversity and disparity across ethnicity and geography. *J Clin Oncol* 2016;34(1):91-101.
18. Vickers AJ, Ulmert D, Sjoberg DD et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. *BMJ* 2013;346(apr15 5):f2023-f2023.
19. Carlsson S, Assel M, Sjoberg D et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. *BMJ* 2014;348:g2296.
20. Hamdy FC, Donovan JL, Lane JA et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375(15):1415-1424.
21. Catalona WJ, Richie JP, Ahmann FR et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 2017;197(2s):S200-S207.
22. Allan RW, Sanderson H, Epstein JI. Correlation of minute (0.5 mm or less) focus of prostate adenocarcinoma on needle biopsy with radical prostatectomy specimen: role of prostate specific antigen density. *J Urol* 2003;170(2):370-372.
23. Catalona WJ, Partin AW, Slawin KM et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA* 1998;279(19):1542-1547.
24. Services C for M& M. Local coverage determination: MolDX: 4Kscore assay (L37122). https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37122&ver=5&DocID=L37122&bc=gAAAABAAAAAA&. Accessed January 23, 2019.
25. Bryant RJ, Sjoberg DD, Vickers AJ et al. Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. *JNCI J Natl Cancer Inst* 2015;107(7)..
26. Nordström T, Vickers A, Assel M, Lilja H, Grönberg H, Eklund M. Comparison between the four-kallikrein panel and prostate health index for predicting prostate cancer. *Eur Urol* 2015;68(1):139-146
27. Barkin J, Rodriguez-Suarez R, Betito K. Association between natural killer cell activity and prostate cancer: a pilot study. *Can J Urol* 2017;24(2):8708-8713.
28. Aubin SMJ, Reid J, Sarno MJ et al. PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial. *J Urol* 2010;184(5):1947-1952.
29. Hessels D, van Gils MPMQ, van Hooij O et al. Predictive value of PCA3 in urinary sediments in determining clinico-pathological characteristics of prostate cancer. *Prostate* 2010;70(1):10-16.
30. Gittelman MC, Hertzman B, Bailen J et al. PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study. *J Urol* 2013;190(1):64-69.
31. Van Neste L, Hendriks RJ, Dijkstra S et al. Detection of high-grade prostate cancer using a urinary molecular biomarker–based risk score. *Eur Urol* 2016;70(5):740-748
32. Kornberg Z, Cooperberg MR, Spratt DE, Feng FY. Genomic biomarkers in prostate cancer. *Transl Androl Urol* 2018;7(3):459-471.
33. McKiernan J, Donovan MJ, O'Neill V et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. *JAMA Oncol* 2016;2(7):882-889.
34. Ankerst DP, Hoefler J, Bock S et al. Prostate cancer prevention trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. *Urology* 2014;83(6):1362-1368.
35. Roobol MJ, Steyerberg EW, Kranse R et al. A risk-based strategy improves prostate-specific antigen–driven detection of prostate cancer. *Eur Urol* 2010;57(1):79-85.
36. Yoo S, Kim JK, Jeong IG. Multiparametric magnetic resonance imaging for prostate cancer: A review and update for urologists. *Korean J Urol* 2015;56(7):487-497.
37. Haider MA, Yao X, Loblaw A, Finelli A. Evidence-based guideline recommendations on multiparametric magnetic resonance imaging in the diagnosis of prostate cancer: A Cancer Care Ontario clinical practice guideline. *Can Urol Assoc J* 2017;11(1-2):E1.
38. Siddiqui MM, Rais-Bahrami S, Turkbey B et al. Comparison of MR/ultrasound fusion–guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015;313(4):390-397.
39. Weinreb JC, Barentsz JO, Choyke PL et al. PI-RADS prostate imaging – reporting and data system: 2015, version 2. *Eur Urol* 2016;69(1):16-40.
40. Barentsz JO, Weinreb JC, Verma S et al. Synopsis of the PI-RADS v2 guidelines for multiparametric prostate magnetic resonance imaging and recommendations for use. *Eur Urol* 2016;69(1):41-49.
41. Dola EF, Nakhla OL, Genidi EAS. Assessing the validity of prostate imaging reporting and data system version 2 (PI-RADS v2) scoring system in diagnosis of peripheral zone prostate cancer. *Eur J Radiol Open* 2017;4:19-26.
42. Takenaka A, Hara R, Ishimura T et al. A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. *Prostate Cancer Prostatic Dis* 2008;11(2):134-138.
43. Eskicorapci S, Guliyev F, Akdogan B, Dogan H, Ergen A, Ozen H. Individualization of the biopsy protocol according to the prostate gland volume for prostate cancer detection. *J Urol* 2005;173(5):1536-1540.
44. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Reports* 1966;50(3):125-128.
45. Epstein JI, Allsbrook WC, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol. 2005;29(9):1228-1242. http://www.ncbi.nlm.nih.gov/pubmed/16096414. Accessed January 23, 2019.
46. Epstein JI, Allsbrook WC, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol* 2005;29(9):1228-1242.
47. Gordetsky J, Epstein J. Grading of prostatic adenocarcinoma: current state and prognostic implications. *Diagn Pathol* 2016;11(1):25.

Androgen deprivation therapy: indications, methods of utilization, side effects and their management

Diana E. Magee, MD,[1] Rajiv K. Singal, MD[1,2]

[1]Division of Urology, Department of Surgery, University of Toronto, Toronto, Ontario, Canada

[2]Division of Urology, Department of Surgery, Michael Garron Hospital, University of Toronto, Toronto, Ontario, Canada

MAGEE DE, SINGAL RK. Androgen deprivation therapy: indications, methods of utilization, side effects and their management. *Can J Urol* 2020; 27(Suppl 1):11-16.

Our objective is to provide an up-to-date summary of current literature on the indications for androgen deprivation therapy (ADT), ways in which ADT is used, and the main side effects associated with its use.

MEDLINE (Pubmed) was searched for relevant papers published from database inception to May 1, 2019 for studies evaluating the use of ADT and its associated adverse events.

ADT is a mainstay in the treatment of prostate cancer and is used throughout the disease course. While predominantly used in the metastatic setting, ADT has a role in the treatment of localized disease and in the management of recurrent cancer. Intermittent ADT has an application for a certain subset of men with recurrent and metastatic disease who have significant side effects. Associated side effects of ADT are wide ranging and include osteoporosis with an associated increased fracture risk, elevated rates of diabetes, metabolic syndrome, cardiovascular risk, sexual dysfunction and hot flashes. As ADT has a variety of associated side effects, care for men receiving ADT is best managed in a multidisciplinary setting with active participation between the treating physician (urologist, radiation oncologist) and their primary care physician.

Key Words: androgen deprivation therapy, indications, management

Introduction

Androgen deprivation therapy (ADT) plays a significant role in the treatment of men with localized, recurrent and metastatic prostate cancer. Almost half of all men treated for prostate cancer receive ADT at some point in their treatment pathway.[1,2] As ADT can cause significant adverse sequalae and negatively impact patient's quality of life it is important for both the treating urologist and family physician to have a comprehensive understanding of anticipated side effects and how best to manage them. This review will summarize the indications for ADT, methods of utilization, and ADT's associated adverse events.

Indications for ADT

Prostate cancer, until the latter stages of the disease, is a hormone sensitive disease. Huggins and Hodges first illustrated the androgen dependency of prostate cancer in 1941 by demonstrating that the androgen blockage achieved through orchiectomy was an effective treatment for symptomatic, metastatic prostate cancer.[3] Since that point in time however, luteinizing hormone-releasing hormone (LHRH) agonists and antagonists have been developed which allow for the medical suppression of testosterone; these agents allow for the reversibility of therapy and avoid the negative physical and psychological effects of orchiectomy.[4-6]

ADT (both LHRH agonists and antagonists), due to prostate cancer's androgen susceptibility, is a mainstay of treatment and can be used at different points in the prostate cancer treatment pathway. In patients with localized disease pursuing curative intent strategies (i.e.: surgery or radiation) ADT has been shown to improve survival when used in conjunction with radiation therapy for patients with intermediate and high-risk disease.[7] Patients with intermediate risk disease are typically given a short course of ADT (4-6 months), while those with high-risk disease are treated for 2-3 years with continuous ADT to help reduce the risk of recurrence through treatment of occult systemic

Address correspondence to Dr. Rajiv K. Singal, Division of Urology, Michael Garron Hospital, 825 Coxwell Avenue, East York ON M4C 3E7 Canada

disease.[8] In patients with non-metastatic, recurrent prostate cancer or localized prostate cancer who are not suitable for curative therapy, ADT should only be used in patients requiring symptom control, when PSA > 50 mg/mL or PSA doubling time < 12 months.[9,10]

The majority of ADT however, is used in the metastatic prostate cancer setting. Patients with metastatic, symptomatic disease require immediate initiation of treatment.[4] However, there are no clear cut offs regarding when to start ADT for those who have documented metastatic disease but remain asymptomatic.[4] A Cochrane review which included four randomized controlled trials (all of which were completed in the pre-PSA era) evaluating immediate versus deferred ADT demonstrated that there was no difference in prostate cancer specific survival between groups although immediate ADT reduced disease progression.[11] The lack of conclusive guidelines is in part due to poorly conducted trials and heterogeneity in study populations which have prevented reliable conclusions to be drawn from their analyses.

Along the disease trajectory, due to long term androgen deprivation, prostate cancer transforms from a hormone sensitive state, in which testosterone blockade is effective at controlling disease, to one that is castrate resistant. At this point, despite low levels of testosterone (testosterone < 50 ng/dL or 1.7 nmol/L), the disease begins to progress. In these cases, additional medications such as docetaxel (chemotherapy), enzalutamide/abiraterone/apalutamide/darolutamide (advanced antiandrogens), radium-223 (bone targeted therapy) are added to the baseline ADT.[4]

Utilization of ADT

Continuous versus intermittent ADT

In the setting of metastatic hormone sensitive prostate cancer, ADT can be administered in either a continuous or intermittent fashion. Initial interest in intermittent ADT was driven by a theory that intermittent androgen deprivation could prolong the time to castrate resistance and thereby lengthen survival.[12] In the largest randomized controlled trial evaluating intermittent versus continuous ADT, the results were inconclusive.[13] As a non-inferiority trial, Hussain et al were unable to rule out a 20% increased risk of death with intermittent therapy compared to continuous. Moreover, of the 3040 patients recruited, only 1535 were eligible for inclusion, illustrating that at best only 50% of patients are candidates for intermittent therapy. A meta-analysis including data from 6856 patients demonstrated no significant difference between intermittent and continuous therapy for overall survival (HR: 1.02; 95%CI: 0.93-1.11), cancer specific survival (HR: 1.02; 95%CI: 0.87-1.19) or progression free survival (HR: 0.94; 95%CI: 0.84-1.05).[14] Patients, did however, report a modest improvement in mental health and sexual function over the short term with intermittent therapy. To better elucidate the durability of benefits seen, Hershman et al reported on long term data from a cohort of patients randomized to intermittent and continuous ADT. Using 10-year incidence rates they found that there was no reduction in bone or endocrine related events but increased incidence of ischemic and thrombotic events.[15] Given the lack of benefit from a survival perspective and conflicting data with respect to adverse events intermittent therapy should be reserved for well-informed patients who have considerable side effects secondary to ADT.

Side effects of ADT and their management:

Bone health

ADT is associated with a decrease in bone mineral density (BMD) as well as an increased risk of fracture. Several prospective studies have shown that BMD decreases by 5%-10% in the first year after starting ADT.[16-19] In retrospective studies using large administrative datasets, ADT use resulted in a small, but statistically significant increase in fracture rates.[20] Smith et al, reported that patients on ADT were at 1.14 times the risk of fracture than those unexposed to ADT after controlling for age, race and incident bone metastases.[21] In a more recent propensity matched retrospective study, patients on ADT were found to have 1.39 times the risk of fractures compared to their unexposed controls.[2] Moreover, the fracture risk increases with longer duration of ADT use.[20]

As a result of the risk of declining BMD secondary to ADT use, existing literature recommends screening for baseline BMD at the time of ADT initiation to allow for risk stratification.[4] A retrospective study from the Veterans Administration demonstrates that only 20% of patients initiated on ADT undergo BMD screening.[22] In a large retrospective study using a administrative database, the involvement of a primary care provider greatly increased the likelihood of BMD testing compared to when a urologist alone cared for the patient.[23] Recognition and management of decreased BMD is important in this patient population since the development of a fracture is associated with decreased overall survival.[24]

Patients on ADT are routinely recommended to supplement their diet with calcium and vitamin D. However, there are no randomized trials that have

demonstrated whether supplementation improves BMD in this population. Currently the National Osteoporosis Foundation recommendations a daily calcium intake of at least 1200 mg (from diet and supplements) and daily vitamin D supplement of 800-1000 IU for all men over the age of 50.[25] These recommendations would seem appropriate for men receiving ADT as well.

Various agents are available to help manage the deleterious bone health effects of ADT. Randomized trials have demonstrated that bisphosphonates are effective at increasing BMD or reducing the loss of BMD in patients on ADT. In a 2001 study evaluating pamidronate 60 mg every 12 weeks, there was a 3.3% decrease in BMD in the lumbar spine, 2.1% in the trochanter and 1.8% in the hip in patients randomized to ADT alone versus those receiving ADT plus pamidronate.[26] In a study evaluating risedronate versus placebo, patients in the placebo arm were found to have decreased BMD versus stable BMD in the risedronate group.[27] A meta-analysis including data from 2634 patients showed treatment with bisphosphonates resulted in increased BMD, whereas patients treated with placebo had decreased BMD.[28] Moreover, the use of bisphosphonates were shown to reduce the risk of fractures (RR: 0.80, $p = 0.005$) and a formal diagnosis of osteoporosis (RR: 0.39, $p < 0.001$).[28]

Denosumab is a human monoclonal antibody directed against RANK-L (receptor activator of nuclear factor kB ligand), which is a key mediator of osteoclast formation, function and survival. A 2009 randomized study found that denosumab increased BMD in the lumbar spine at 2 years by 5.6% compared with a 1% loss in the placebo group ($p < 0.001$).[29] Similar improvements in BMD were seen in the hip, femoral head and radius. Moreover, denosumab use led to decreased vertebral fractures at 3 years (1.5% versus 3.9%; RR: 0.38; 95%CI: 0.19-0.78; $p = 0.006$).

As men who receive ADT experience greater BMD loss than normal and are therefore at higher risk for fractures, current National Comprehensive Cancer Network guidelines suggest ensuring adequate intake of calcium and vitamin D and obtaining a baseline BMD test to determine baseline risk for patients on long term ADT.[30] In one study the provision of focused education on bone health was associated with a trend towards improved adherence to vitamin D and calcium intake.[31] Further treatment with bisphosphonates (aldendronate, zoledronic acid) or denosumab is recommended for men with a T score ≤ -2.0 at the lumbar spine, femoral neck or hip or if the 10-year risk of fracture is greater than 20% for any major fracture or greater than 3% for hip fracture.[30]

Metabolic consequences

The use of ADT has known metabolic consequences. This is supported by both prospective and population level evidence. Several small, prospective studies found that the use of ADT was associated with weight gain, increased body fat percentage, greater insulin resistance and elevated fasting glucose levels.[32-34]

The link between ADT use and diabetes risk raised by the smaller, initial studies was later confirmed by several large population-based studies. In one study, the US-based SEER-Medicare database was used, including over 70,000 men over the age of 65 with prostate cancer; they found a 44% increased risk of incident diabetes in the cohort being treated with ADT.[35] Another study using the Veterans Administration database, reported similar findings; in men treated with ADT there was a 28% increased risk of incident diabetes.[36] Finally, using an administrative database from Ontario, Canada over 19,000 men over the age of 66 treated with > 6 months of ADT or bilateral orchiectomy were examined.[37,38] The receipt of ADT or bilateral orchiectomy was associated with an increased risk of diabetes (HR: 1.24; 95%CI: 1.15-1.35).

The diagnosis of metabolic syndrome requires the presence of three of five criteria: 1) serum triglycerides > 150 mg/dL (1.7 mmol/L), 2) high density lipoprotein (HDL) < 40 mg/dL (1.0 mmol/L), 3) fasting serum glucose > 110 mg/dL (6.1 mmol/L), 4) waist circumference > 102 cm, and 5) blood pressure ≥ 130/85.[39] ADT has been shown to increase waist circumference secondary to weight gain and risk of diabetes. Triglycerides have also been shown to be affected by ADT; triglycerides of patients on ADT increased by 26.5% (± 10%; $p = 0.01$) after 1 year of treatment.[32] Metabolic syndrome as a composite outcome was assessed by Braga-Basaria et al, illustrating that metabolic syndrome was present in more than 50% of patients treated with long term ADT. The main drivers of the metabolic syndrome diagnosis were abdominal obesity, hyperglycemia, and elevated triglycerides.[40]

The impact of exercise in the setting of ADT has been evaluated. Galvao et al conducted a randomized, multicentre trial evaluating supervised exercise versus physical activity with printed material in men previously treated with ADT. Improvements were seen in cardiovascular fitness, muscle strength, and self-reported physical functioning.[41] However, no significant differences were found between groups with respect to total body weight or waist circumference. The patients receiving supervised exercise sessions had increased HDL levels at 1 year (0.13 mmol/L; $p = 0.001$). As a result of this and other smaller studies which showed mixed results,[42,43] it is not entirely clear what degree

of benefit is derived from exercise in the prevention or treatment of metabolic syndrome. However, the recommendation for routine physical activity is sensible.

Due to the increased risk of insulin resistance and incident diabetes while receiving ADT, these men could be considered high risk and thus screened as such.[44] Regular blood glucose monitoring of patients with pre-existing diabetes to ensure adequate control is maintained would also be prudent. Triglyceride abnormalities should be treated as per guidelines to minimize cardiovascular risk.

Cardiovascular disease

The link between ADT and cardiovascular disease has evolved over the past two decades. The first study to evaluate the association was a SEER-Medicare study which evaluated over 70,000 men with prostate cancer.[35] Keating et al found that men receiving LHRH agonists had a 16% increased risk of coronary heart disease, an 11% increased risk of myocardial infarction (MI) and a 16% increased risk of sudden cardiac death compared to prostate cancer patients not on ADT. The association between ADT and increased cardiovascular risk was reproduced in a later study which showed that patients with newly diagnosed prostate cancer receiving LHRH agonists experienced a 20% increase in cardiovascular mortality over a 5 year follow up period.[45] These publications led to a FDA imposed modification of ADT drug labels to include the risk of cardiovascular outcomes secondary to therapy.[46]

However, not all studies reproduced evidence of this association. Alibhai et al retrospectively evaluated records for approximately 20,000 men in Ontario and did not find evidence of an association between ADT and acute MI (HR: 0.91; 95%CI: 0.84-1.00) or sudden cardiac death (HR: 0.96; 95%CI: 0.83-1.10).[37] Furthermore, four post-hoc analyses of randomized controlled trials reported no association between ADT and cardiovascular mortality.[47-50] These findings were supported by a meta-analysis of eight randomized controlled trials which found that there was no difference in risk of CV death in patients receiving ADT versus those who did not (RR: 0.93; 95%CI: 0.79-1.10; p = 0.41).[51]

The relationship between ADT and cardiovascular events has also been examined accounting for a patient's baseline cardiovascular risk. Two retrospective studies found that ADT use was associated with increased risk of all-cause mortality only among patients with a previous myocardial infarction or diagnosis of congestive heart failure.[52,53] However, this link is not definitive as a large SEER-Medicare study found that baseline comorbidity did not modify impact of ADT on the risk of MI[54] and re-analysis of two randomized trials stratifying by morbidity did not find that men with pre-existing cardiovascular disease had excess cardiovascular deaths.[48,49]

The difficulty in interpreting these conflicting studies stems from the heterogeneity of patient populations, outcome definitions and study design. The only studies to show a relationship between ADT and increased cardiovascular risk feature observational designs whereas, no re-analysis of randomized trial data has yielded evidence of an association. However, no clinical trial was specifically designed to evaluate cardiovascular risk and therefore the limitations inherent to post hoc analyses must be appreciated. The mechanism for association between ADT and cardiovascular disease may be linked to metabolic effects which have been more conclusively delineated. Therefore, management of metabolic syndrome may help to mitigate increased cardiovascular risk if there is a true association.[44]

In the above-mentioned trials, the majority of patients were receiving LHRH agonists and therefore studies have sought to determine if LHRH antagonists may have a different risk profile. A pooled analysis including six randomized trials of degarelix (LHRH antagonist) versus leuprolide (LHRH agonist) found that degarelix was associated with a lower risk of cardiovascular events (HR: 0.60; 95%CI: 0.38-0.94; p = 0.025); degarelix was found to be even more protective in patients with baseline cardiovascular disease compared to leuprolide (HR: 0.476; 95%CI: 0.260-0.871; p = 0.016) (55). Care should be taken when interpreting these results since it was a post hoc analysis, but it suggests that for patients with baseline cardiovascular disease, LHRH antagonists may be the preferred method of testosterone suppression.

Sexual dysfunction:

Sexual dysfunction affects over 90% of men receiving ADT.[56] For patients who have already received primary therapy, sexual function may already be significantly affected, and the addition of ADT further exacerbates pre-existing problems. ADT, because its very nature of sharply reducing testosterone levels, is associated with a decrease in sexual desire and erectile function.[44] Limited options are available to mitigate the sexual side effects of ADT. Intermittent ADT, by allowing for testosterone recovery in between treatment cycles, may allow a select group of patients reprieve from the sexual side effects. Crook et al demonstrated that men on intermittent therapy had greater desire for sexual activity compared to men on continuous therapy[57] and Hussain et al demonstrated that erectile function

was significantly better in the intermittent group.[13] However, intermittent therapy is not suitable for all patients and the trade off between adverse sexual side effects and oncological control needs to be balanced.

Hot flashes

Hot flashes, described as sudden sweating and facial discomfort, affect up to 80% of patients treated with ADT.[58] For some patients, these flashes are debilitating while for others they are simply a nuisance. Conservative management is initially the first recommendation for management of hot flashes including limiting exposure to potential triggers (i.e.: heating, or spicy foods).[59] Various medications are available to reduce the frequency and severity of hot flashes. A randomized controlled trial demonstrated that venlafaxine, cyproterone acetate and medroxyprogesterone all led to improvements within 1 month of initiation and can be considered for bothersome symptoms.[60]

Conclusion

ADT is an important treatment modality in the management of prostate cancer. However, it is known to be associated with a variety of potential negative sequalae. The impact of ADT on bone health, metabolic syndrome risk, cardiovascular disease risk, sexual function and the development of hot flashes has been illustrated. Strategies for mitigating adverse side effects are available but require a wide range of expertise to do so effectively. A model of collaborative care that includes a patient and his partner, his urologist, radiation oncologist and family physician can help to optimize outcomes in treating men with prostate cancer. □

References

1. Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer* 2005;103(8):1615-1624.
2. Nguyen C, Lairson DR, Swartz MD, Du XL. Risks of major long-term side effects associated with androgen-deprivation therapy in men with prostate cancer. *Pharmacotherapy* 2018;38(10):999-1009.
3. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *J Urol* 2002;168(1):9-12.
4. Cornford P, Bellmunt J, Bolla M et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol* 2017;71(4):630-642.
5. Crawford ED, Shore ND, Moul JW et al. Long-term tolerability and efficacy of degarelix: 5-year results from a phase III extension trial with a 1-arm crossover from leuprolide to degarelix. *Urology* 2014;83(5):1122-1128.
6. Van Poppel H, Klotz L. Gonadotropin-releasing hormone: an update review of the antagonists versus agonists. *Int J Urol* 2012;19(7):594-601.
7. Mottet N, Bellmunt J, Bolla M et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71(4):618-629.
8. Bolla M, Van Tienhoven G, Warde P et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010;11(11):1066-1073.
9. Studer UE, Collette L, Whelan P et al. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). *Eur Urol* 2008;53(5):941-949.
10. van den Bergh RC, van Casteren NJ, van den Broeck T et al. Role of hormonal treatment in prostate cancer patients with nonmetastatic disease recurrence after local curative treatment: a systematic review. *Eur Urol* 2016;69(5):802-820.
11. Nair B, Wilt T, MacDonald R, Rutks I. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. *Cochrane Database Syst Rev* 2002(1):CD003506.
12. Akakura K, Bruchovsky N, Goldenberg SL, Rennie PS, Buckley AR, Sullivan LD. Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. *Cancer* 1993;71(9):2782-2790.
13. Hussain M, Tangen CM, Berry DL et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med* 2013;368(14):1314-1325.
14. Magnan S, Zarychanski R, Pilote L et al. Intermittent vs continuous androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *JAMA Oncol* 2015;1(9):1261-1269.
15. Hershman DL, Unger JM, Wright JD et al. Adverse health events following intermittent and continuous androgen deprivation in patients with metastatic prostate cancer. *JAMA Oncol* 2016;2(4):453-461.
16. Maillefert JF, Sibilia J, Michel F, Saussine C, Javier RM, Tavernier C. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J Urol* 1999;161(4):1219-1222.
17. Berruti A, Dogliotti L, Terrone C et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* 2002;167(6):2361-2367; discussion 7.
18. Goldray D, Weisman Y, Jaccard N, Merdler C, Chen J, Matzkin H. Decreased bone density in elderly men treated with the gonadotropin-releasing hormone agonist decapeptyl (D-Trp6-GnRH). *J Clin Endocrinol Metab* 1993;76(2):288-290.
19. Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, Stratte PT. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *J Urol* 2000;163(1):181-186.
20. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352(2):154-164.
21. Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol* 2005;23(31):7897-7903.
22. Kirk PS, Borza T, Shahinian VB et al. The implications of baseline bone-health assessment at initiation of androgen-deprivation therapy for prostate cancer. *BJU Int* 2018;121(4):558-564.
23. Shahinian VB, Kuo YF. Patterns of bone mineral density testing in men receiving androgen deprivation for prostate cancer. *J Gen Intern Med* 2013;28(11):1440-1446.

24. Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J Urol* 2002;168(3):1005-1007.
25. Foundation NO. Clinician's guide to prevention and treatment of osteoporosis [Available from: http://www.nof.org/files/nof/public/content/file/344/upload/159.pdf.
26. Smith MR, McGovern FJ, Zietman AL et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001;345(13):948-955.
27. Choo R, Lukka H, Cheung P et al. Randomized, double-blinded, placebo-controlled, trial of risedronate for the prevention of bone mineral density loss in nonmetastatic prostate cancer patients receiving radiation therapy plus androgen deprivation therapy. *Int J Radiat Oncol Biol Phys* 2013;85(5):1239-1245.
28. Serpa Neto A, Tobias-Machado M, Esteves MA et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2012;15(1):36-44.
29. Smith MR, Egerdie B, Hernandez Toriz N et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361(8):745-755.
30. Gralow JR, Biermann JS, Farooki A et al. NCCN task force report: bone health in cancer care. *J Natl Compr Canc Netw* 2013;11(Suppl 3): S1-50; quiz S1.
31. Tsang DS, Jones JM, Samadi O et al. Healthy bones study: can a prescription coupled with education improve bone health for patients receiving androgen deprivation therapy?-a before/after study. *Support Care Cancer* 2018;26(8):2861-2869.
32. Smith MR, Finkelstein JS, McGovern FJ et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab* 2002;87(2):599-603.
33. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 2006;91(4):1305-1308.
34. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer* 2006;106(3):581-588.
35. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24(27):4448-4456.
36. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst* 2010;102(1):39-46.
37. Alibhai SM, Duong-Hua M, Sutradhar R et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol* 2009;27(21):3452-3458.
38. ERRATUM. *J Clin Oncol* 2009;27(29):4927.
39. Alberti KG, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120(16):1640-1645.
40. Braga-Basaria M, Dobs AS, Muller DC et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol* 2006;24(24):3979-3983.
41. Galvao DA, Spry N, Denham J et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol* 2014;65(5):856-864.
42. Carmack Taylor CL, Demoor C, Smith MA et al. Active for Life After Cancer: a randomized trial examining a lifestyle physical activity program for prostate cancer patients. *Psychooncology* 2006;15(10):847-862.
43. Santa Mina D, Alibhai SM, Matthew AG et al. A randomized trial of aerobic versus resistance exercise in prostate cancer survivors. *J Aging Phys Act* 2013;21(4):455-478.
44. Nguyen PL, Alibhai SM, Basaria S et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015;67(5):825-836.
45. Saigal CS, Gore JL, Krupski TL et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 2007;110(7):1493-1500.
46. Administration UFaD. FDA drug safety communication: Update to ongoing safety review of GnRH agonists and notification to manufacturers of GnRH agonists to add new safety information to labeling regarding increased risk of diabetes and certain cardiovascular diseases.
47. Roach M 3rd, Bae K, Speight J et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008;26(4):585-591.
48. Efstathiou JA, Bae K, Shipley WU et al. Cardiovascular mortality and duration of androgen deprivation for locally advanced prostate cancer: analysis of RTOG 92-02. *Eur Urol* 2008;54(4): 816-823.
49. Efstathiou JA, Bae K, Shipley WU et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol* 2009;27(1):92-99.
50. Studer UE, Whelan P, Albrecht W et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol* 2006;24(12):1868-1876.
51. Nguyen PL, Je Y, Schutz FA et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *JAMA* 2011;306(21):2359-2366.
52. Nguyen PL, Chen MH, Beckman JA et al. Influence of androgen deprivation therapy on all-cause mortality in men with high-risk prostate cancer and a history of congestive heart failure or myocardial infarction. *Int J Radiat Oncol Biol Phys* 2012;82(4):1411-1416.
53. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. *JAMA* 2009;302(8):866-873.
54. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Does comorbidity influence the risk of myocardial infarction or diabetes during androgen-deprivation therapy for prostate cancer? *Eur Urol* 2013;64(1):159-166.
55. Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol* 2014;65(3):565-573.
56. Higano CS. Sexuality and intimacy after definitive treatment and subsequent androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2012;30(30):3720-3725.
57. Crook JM, O'Callaghan CJ, Duncan G et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367(10):895-903.
58. Walker LM, Tran S, Robinson JW. Luteinizing hormone--releasing hormone agonists: a quick reference for prevalence rates of potential adverse effects. *Clin Genitourin Cancer* 2013;11(4):375-384.
59. Rhee H, Gunter JH, Heathcote P et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int* 2015;115(Suppl 5):3-13.
60. Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol* 2010;11(2): 147-154.

Management of erectile dysfunction and LUTS/ incontinence: the two most common, long-term side effects of prostate cancer treatment

Valentin Shabataev, MD, Seyed Hossein Saadat, MD,
Dean S. Elterman, MD
Division of Urology, University Health Network, University of Toronto, Toronto, Ontario, Canada

SHABATAEV V, SAADAT SH, ELTERMAN DS. Management of erectile dysfunction and LUTS/ incontinence: the two most common, long-term side effects of prostate cancer treatment. *Can J Urol* 2020;27(Suppl 1):17-24.

The two major long-term concerns associated with different options for the management of prostate cancer, (including surgery, radiotherapy, brachytherapy, cryotherapy, HIFU, etc.) include difficulties with lower urinary tract symptoms (LUTS) and/or erectile dysfunction.

LUTS can be in the form of stress urinary incontinence (SUI), urge urinary incontinence (UUI), frequency/ urgency, and/or voiding difficulties. While surgery is mostly associated with SUI and radiation mostly results in UUI, there can be an overlap. Incontinence rates after cryotherapy and high intensity focused ultrasound (HIFU) are generally very low. Voiding difficulties can also happen after the above-mentioned options.

Treatment of SUI can start with pelvic floor muscle exercises (PFME), penile clamps or urethral plugs. If these fail to provide satisfactory results the surgical options could include: urethral bulking agents, male slings, and artificial urinary sphincter (AUS). Surgical options are usually not recommended during the first 6-12 months after radical prostatectomy.

Management of frequency, urgency and/or UUI can also be started with lifestyle modifications and PFME. Oral agents (anticholinergics and β3-agonists) are also considered before proceeding to third line options, such as Botox injection or sacral neuromodulation.

The treatment options for ED resulting from the treatment of prostate cancer can include oral PDE5-I as the first line, local therapy as the second (such as MUSE, intracavernosal injections, and perhaps low intensity shock wave therapy) and finally surgery as the third line. Standard questionnaires and patient reported outcome measurement tools should be used for the assessment of LUTS and erectile dysfunction prior and after initiation of treatment to guide the management.

Key Words: LUTS, incontinence, prostate cancer, management

Introduction

Management of prostate cancer continues to evolve towards ever more favorable oncologic outcomes. In this context, the patients' quality of life has become of primary importance as part of their cancer survivorship. Regardless of the treatment modality chosen for prostate cancer (radical prostatectomy, brachytherapy, external radiation therapy, high intensity focused ultrasound (HIFU), cryotherapy, etc.), two main complications following treatment include bothersome lower urinary tract symptoms (LUTS) and erectile dysfunction.

Address correspondence to Dr. Dean Elterman, Division of Urology, Toronto Western Hospital, 399 Bathurst Street, Main Pavilion, Room 8-317, Toronto ON M5T 2S8 Canada

Urinary incontinence

Although it is generally believed that new techniques for nerve-sparing radical prostatectomy (RP) have helped to reduce the incidence of post-prostatectomy urinary incontinence, the reported incontinence rates are widely different and may reach figures as high as 69%, depending on definitions and questionnaires used.[1,2] The widely accepted definition of post-prostatectomy incontinence (PPI) is a persistent stress urinary incontinence (SUI) over 1 year after prostatic surgery, assuming conservative therapy failure.[3] Having said that, SUI is not the only type of incontinence after RP and patients can also experience urge urinary incontinence (UUI). According to latest reports, 29% of patients experience storage symptoms after RP and 6% report urgency urinary incontinence.[4]

The etiology of post-prostatectomy incontinence (PPI) can be multifactorial. These include mechanisms that affect sphincteric function or those that affect bladder function (resulting in impaired bladder compliance, detrusor over- or underactivity). Among these two, sphincter insufficiency is assumed to be the most important reason for incontinence after RP, resulting in SUI.[5,6] Many factors such as age or history of transurethral resection of the prostate (TURP), can influence the continence rate after RP.[2]

Radiotherapy (RT) can also damage bladder wall function through impairment of blood circulation due to endarteritis within the detrusor with subsequent apoptosis and ultimately tissue loss.[7] These differences in pathophysiology are reflected in clinical features of LUTS following radiotherapy. In other words, while RP mostly causes SUI (starting in the early period after the operation), urinary symptoms following RT usually manifest as overactive bladder symptoms such as frequency, urgency or urge urinary incontinence (UUI). Brachytherapy can also cause LUTS. One large study of 2461 men after brachytherapy with or without external radiation showed that during 6.4 years of follow up, the incidence of UUI was about three times the incidence of SUI.[8] Patients who have received RT can also experience bladder outlet obstruction with symptoms such as hesitancy, weak urinary stream and intermittency. These can progress until 5 years after external radiotherapy or brachytherapy.[7,9] Later complications of RT can include urethral strictures, leading to urinary retention, and hematuria due to radiation cystitis.

Incontinence rates after cryotherapy and high intensity focused ultrasound (HIFU) are generally low and mostly depend on the volume of ablation (focal versus whole gland ablation). According to the report from the national Cryo On-Line Database (COLD) registry which contained information on 5853 patients, the rate of urinary incontinence after cryotherapy is 1.6% for focal ablation and 3.1 for whole gland ablation.[10] Similar degree of incontinence after HIFU was reported by several studies.[11,12]

Treatment of urinary incontinence depends on its clinical appearance (SUI versus UUI and OAB symptoms), regardless of prostate cancer treatment modality. The treatment options for SUI can be generally divided into two categories of conservative versus surgical options. Conservative methods such as pelvic floor muscle exercises, pad use, penile clamps or urethral plugs are considered the first line of treatment. If these fail to provide satisfactory results the surgical options could include: urethral bulking agents, male slings, and artificial urinary sphincter (AUS). Surgical options are usually not recommended during the first 6-12 months after RP, to allow for spontaneous recovery and maximum improvement of continence. Following the initial period, repeated assessment of incontinence severity helps to make a decision and to choose a certain type of surgical option. While urethral bulking agents and sling operations are suitable for mild to moderate cases of SUI, the AUS is recommended for more severe incontinence. Both pelvic floor muscle exercises and pharmacotherapy can be considered for overactive bladder (OAB) symptoms including UUI.

Pelvic floor muscle exercise

Pelvic floor muscle training (PFMT) is defined as "any program of repeated voluntary PFM contractions taught by a health-care professional." It is well understood by urologists that PFMT improves urethral stability and increases urethral closure pressure, which in turn helps with the improvement of SUI. Interestingly this is a treatment modality that can also improve OAB symptoms, including UUI, by inhibiting involuntary detrusor contractions (IBC). Patients may undergo office biofeedback or be referred to a physiotherapist who specializes in the pelvic floor. After providing appropriate instructions, patients can continue with PFME without any medical assistance. Unfortunately not everyone responds to PFMT.[13] According to the recent Cochrane report of 2736 patients treated by PFME for post-prostatectomy incontinence, there was only moderate evidence for an overall benefit from PFMEs compared with the control group.[14] Another interesting conclusion was obtained in a recent meta-analysis of PFME programs. The relative risk of continence in the PFME group versus control group was 2.16 at 3 months postoperatively. While at 12 months postoperatively this rate was reduced to 1.23. This indicates that PFME during the first year only helps to reach the maximum possible improvements faster.[15]

Penile compression device (penile clamp) for SUI

During the first 6-12 months after RP, or in patients who are not willing to have another surgery for correction of their SUI, or those who are not fit for additional operations penile compression devices are suitable options. They are available in different designs and sizes and can be purchased anonymously. The clamp is placed around the penis and mechanically compresses the urethra. Use of penile clamps help

to reduce the Incontinence Impact Questionnaire scores.[16] Although none of them completely eliminated urine loss, the devices are well tolerated and improve patients' confidence and tolerance of physical activity. However, complications such as pain, urethral erosion, obstruction, and edema have been reported with long term use.[17] These devices should be used only in men who have normal penile skin and who have sufficient cognitive function and dexterity to open and close the device. Also, the patients have to be instructed to remove the clamp in regular (2-3 hourly) intervals to empty the bladder and restore blood flow in the penis.[16] An alternative containment strategy includes the use of condom catheters. A specially designed condom with inner adhesive may be rolled onto a flaccid penis and the open end can drain into tubing connected to a leg bag.

Pharmacotherapy

Although it is generally believed that urinary incontinence after RP is a result of damage to the urinary sphincter mechanism and no medications have proven to restore this function, there is evidence of additional lower urinary tract disorders, which may play at least a small part in incontinence. Those include impaired compliance and detrusor overactivity (DO).[18] The rationale of pharmacotherapy is based on improving these disorders. Antimuscarinic drugs, β3 agonists and duloxetine have been proposed as medical treatments for these scenarios.[19]

Antimuscarinic and β3 agonists medication, are known as the second-line treatment for DO after PFMT, and may also be used in mixed urinary incontinence. The literature search identified a limited number of studies regarding the use of antimuscarinic medications after prostate cancer treatment; however, one can assume these medications to be also effective in treating OAB symptoms after prostate cancer treatment. The largest randomized double-blind study was in 640 patients. Patients were randomized to solifenacin 5 mg daily or placebo for 12 weeks in an early post-prostatectomy period. In results, the continence rate was 29% in the treatment group versus 21% in the placebo group.[20] Mirabegron (Myrbetriq) is a β3 agonist, with efficacy similar to antimuscarinics but with fewer side effects. There is no data available on its use in the post-prostate cancer population.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor with influence on Onuf's nucleus in the sacral spinal cord. It provides stimulation of the pudendal nerve, increasing tonus of urethral sphincter and relaxing the detrusor muscle. Duloxetine has been mostly studied in treatment of female stress incontinence. According to most studies where duloxetine was investigated as a treatment option for post RP incontinence during the first 12 months, continence rates were similar to PFME or showed minimal additional effect. The most common reported side effects of duloxetine are fatigue, dry mouth, nausea, and constipation with controversial reports about discontinuation rates.[19]

In conclusion, there is not enough evidence to recommend the use of these medications as a standard treatment of post-prostate cancer treatment incontinence.

Surgical treatment (for SUI, frequency/urgency, and/or UUI)

When conservative treatment fails, surgery is still the treatment of choice, although there is no accepted guideline on when surgical treatment should be performed. Currently artificial urinary sphincter (AUS) is considered as the gold standard treatment for patients suffering from post-prostate cancer treatment incontinence. This is based on multiple studies showing acceptable long-term success rates among the other options. Other options, such as bulking agents and male slings can be applied as less invasive alternatives in selected patients. The most important factor for choosing among these surgical options is the severity of incontinence. In order to determine the degree of incontinence, some authors suggest using pad weight test, so-called 24 h pad test, to determine the degree of incontinence. To make the right decision about surgical treatment options, it has been generally accepted to divide the incontinence into mild (< 100 gm/24 hours), moderate (100-400 gm/24 hours) and severe (> 400 gm/24 hours). However, variation in activity level can lead to significant differences in 24 hour pad weights from one day to another and that is why many physicians refused the test and continue to rely on the patient's description of pad number and wetness.[21] Indeed, the size and type of pad and frequency of pad exchanging may be variable, but this information, received from the patient, helps to recognize his perception of the severity of incontinence. For example, if a patient uses several large pads or diapers, which are always wet, that may indicate severe incontinence. In contrast, wearing one or a few small pads per day can be classified as mild or mild-moderate incontinence.[22]

In a recent US national database study of 1246 patients who were operated upon due to SUI, it was shown that 34.9% of patients received an AUS, 36.4% were treated with urethral slings, and 28.7% received a urethral bulking agent.[23]

To date, the AMS 800 is the most commonly used artificial urinary sphincter (Boston Scientific, Marlborough, MA, USA). This AUS is made up of three parts: urethral cuff which wraps around the urethra to control the flow of urine; a pump which is placed in the scrotum and helps to move fluid into or away from the urethral cuff; and a balloon or reservoir which holds the fluid when the urethral cuff is deflated, which is placed beneath abdominal muscles. Reported continence rates vary between different studies from 55% to 86%.[1] These disparities resulted from lack of universal definition of treatment success as well as a different number of patients with negative predictive features such as radiation or cryotherapy as an etiology of incontinence.[24,25] Despite high rates of patient satisfaction, it has a risk of unique AUS complications including the risk of infection (up to 16%), urethral erosion (up to 13 %) and mechanical failure (up to 6.3%).[1,26,27] The second common AUS device ZSI 375, recently introduced in clinical practice, has reported a similar success rate.[28] But in contrast to AMS 800 it does not have the balloon (reservoir) and therefore does not require an additional abdominal incision. For that reason it has a lower risk of mechanical failures (3.4%).[28]

In the last decades, synthetic mesh male slings (MS) for SUI have become more popular due to its lower cost, less invasiveness and due to the fact that they do not require mechanical manipulation while voiding. The success rate varies from 50% to 90%[29-32] according to the definition of continence and type of device. Even though this outcome seems similar to the success rate of AUS, it has to be kept in mind that MS study cohorts have been different from AUS cohorts. Most urologists concluded that in order to improve the outcomes, careful patient selection is obligatory. The proper candidate should have a mild to moderate degree of SUI, adequate detrusor contraction with no history of radiation treatment in the pelvic area.[33]

The MS can be divided into adjustable or non-adjustable types which in turn divided into several subtypes determined by fixation mechanism and anatomical position.[33] The adjustable MS can be easily modified to elevate the urethral compression if incontinence does not resolve. With this rationale, it has at least a theoretical advantage over non-adjustable MS. However, no significant differences have been observed in the clinical outcomes or patient satisfaction rates when comparing these devices.[29,30]

At the present time, the AdVance XP sling (Boston Scientific, Marlborough, MA, USA) is the most frequently worldwide used retro-urethral trans-obturator sling which consists of a polypropylene mesh that is placed under the membranous urethra through a trans-obturator approach.[33] The concept of the urethral sling is to reposition the bulbar urethra by a distance of 3-4 cm which produces additional functional resistance to the posterior urethra and provides support for the external sphincter complex.[34]

The overall complication rate for the AdVance sling was reported at 12.3%. Major early postoperative complications include transient urinary retention requiring temporary re-catheterization (2.7%-15.1%), local infection (1.7%-6.4%) and perineal pain (4%-17%). Late complications are mesh erosions (1.9%-12.8%) into bladder or urethra that are most commonly found in patients who have received radiation therapy.[35]

Another type of inflatable continence devices called ProACT consists of two silicone balloons on the proximal end and a titanium port in the distal end. The two balloons are implanted just below the bladder neck, one on each side, through a trans-cutaneous access in the perineal area under fluoroscopy or trans-rectal ultrasound guide. The balloons can be inflated or deflated to compress the urethral lumen just below the bladder neck.[33] The technical ease of insertion and the lack of circumferential urethral dissection are proposed advantages of ProACT device. Despite the initial high cure rate, more than a third of patients were dissatisfied with the surgical outcome in the long term. In one long term study, it has been found that only 45% of patients remained satisfied with ProACT device at a median follow up of 57 months.[36] However, given its minimally invasive nature, this device may provide some benefit for additional improvement of continence in case of persistent or recurrent incontinence after sling implantation. Common complications of ProACT device include balloon migration, pain, infection, and recurrent incontinence.

Several types of bulking agents have been proposed for SUI, such as macroplastique, collagen, bulkamide hydrogel and dextranomer/hyaluronic acid copolymer. In the case of post–prostate cancer treatment incontinence, they are injected submucosally in the anastomosis region in an attempt to enhance coaptation of the urethra.[19] In general, these agents have been shown to have low and short lasting effects and recommended in very certain scenarios. One of these indications is recurrent or persistent incontinence after male sling operations. In this case, 80% of men required no further treatment for PPI. Given its low invasive nature, only low-grade complications were reported in 10% of patients.[37]

Surgical options for the management of OAB symptoms could include botox injection or sacral neuromodulation. The details of these options are out of scope of this article.

Erectile dysfunction

Erectile dysfunction (ED) after treatment of prostate cancer is a significant quality of life problem for patients and their healthcare providers.

One of the "gold standard" treatment options for localized prostate cancer is RP, which has established long term oncologic benefits.[38] ED is a common side effect of the surgery, and given the trend towards being younger at the time of diagnosis and treatment with excellent survival rates, ED becomes a primary concern after RP for many men. The literature reports have a wide variation in erectile function recovery (EFR) rate following RP. In one previous meta-analysis of 22 relevant studies, the rate of EFR ranged from 25% to 78% in an 18 month follow up period after RP. Open RP and traditional laparoscopic RP had similar EFR (57% versus 58%), while robot-assisted RP resulted in a higher EFR rate, 73% compared with these other approaches. Patients < 60 years old had a higher EFR rate than patients ≥ 60 years, with EFR being 77% versus 61% respectively.[39] In a more recent study, the authors used more strict definitions of ED and assessed the number of patients who returned to having baseline erections after RP during 24 months without the use of any medications for ED and compared the results before and after RP. They found that only 22% of patients returned to their baseline erectile function (EF) without the use of medication. Of note, only 4% of men who were ≥ 60 years of age with functional erections prior to surgery achieved their baseline EF without the use of medication.[40]

The introduction of robotic surgery has led to further evolution of the RP technique. This allows for more precise identification of the periprostatic fascia, thus providing a higher degree of preservation of the periprostatic neurovascular tissue. While most studies have shown a higher EFR rate in robotic surgery, a recent study from a high-volume center, has shown that EFR has not changed over the last decade. With the recovery rates during the last decade being 27% and 34% at 1 and 2 year post-RP respectively.[41]

The second common type of prostate cancer treatment is radiation therapy (RT), which can be external or internal (brachytherapy) radiation with different modalities and radiation dose rates. In contrast to radical prostatectomy, where ED is evident soon after the operation, radiation-based treatments lead to slowly declining EF over 1 to 3 years. Survival rates of prostate cancer patients are high and within 3-5 years of completing treatment, approximately one-half of these patients will develop ED.[42] There are several new techniques for external RT that allow for the delivery of higher doses of radiation with better cancer control rates and fewer side effects, such as intensity-modulated radiation therapy (IMRT) or stereotactic radiation therapy. However, according to several reports, EFR rates were not much different from rates following different types of external RT or brachytherapy.[42,43]

In brief, erection is achieved through five phases: initial filling, partial erection, full erection, rigid erection, and return to flaccid state. Psychological or physical sexual stimulation leads to smooth muscle relaxation of the arteries, which allows an increase in blood flow to the corpora cavernosa. Full erection occurs when full rigidity is obtained. During a return to a flaccid state, muscle contractions result in the increased venous outflow and decreasing penile length and girth.[44] Supposed mechanisms of ED after RP or RT rely on neuronal and vascular damage, which can lead to ED through smooth muscle atrophy of the corpora cavernosa, similar to other muscles that atrophy when they are unused.[42] Both in-vitro and in-vivo studies support the theory that penile hypoxia results in collagen accumulation, smooth-muscle apoptosis and ultimately cavernosal fibrosis. Finally, these changes within the corpus cavernosum contribute to venous leakage and permanent ED, even if the normal function of the nerves return.[45]

Ablative therapy (whole gland or focal) was introduced with the hope of avoiding some of the adverse effects of radical therapy including ED, bladder or bowel dysfunction and urinary incontinence. Ablative therapies refer to a group of minimally invasive modalities, which aim for either total, subtotal or focal ablation (or destruction) of the prostate gland. Currently, apart from cryotherapy and HIFU, which have been investigated within the context of clinical trials, none of the others have been used in daily practice.[46] Currently, ED rates after ablative therapy is not interpretable, as many studies within the existing literature either use their own definitions of ED or use no definition at all.[47] Cryotherapy was one of the first ablative techniques to be introduced. It induces cell lysis by cooling tissues down to –40°C. Autonomic dysfunction occurs if the nearby neurovascular tissue reaches 20°C, which may explain the high rates of ED observed after cryotherapy. With HIFU, focused ultrasound energy results in tissue ablation via thermal coagulation, necrosis, and acoustic cavitation. It has the potential of more precise ablation than cryotherapy but many men report ED nevertheless.[48]

In a study that compared cryotherapy with HIFU in cases of whole gland ablation in patients with good pretreatment EF, there was a significant fall in International Index of Erectile Function (IIEF-5) in

both groups at 6 months. The fall from baseline was statistically greater for whole gland cryotherapy than whole gland HIFU at all time follow up points. There was a minimal improvement from the initial fall in IIEF-5 during the 24 months for both modalities.[12] On the other hand, focal ablation has a less detrimental effect on EF.[49] Interestingly, in one non-randomized comparative study, the whole gland HIFU was found to be associated with better EF than both focal and whole gland cryotherapy.[12] In a recent meta-analysis of ablative therapy outcomes, five cryotherapy studies and only two HIFU studies provided information on ED. In cases of cryotherapy, the data showed a lower rate of ED compared to those receiving RP at 1 year, but the difference was not statistically significant. However, analysis of the above mentioned HIFU studies showed a statistically less ED following HIFU comparing to RP.[46]

The treatment options for ED in post-prostate cancer treatment patients are not different from the options for common ED. Traditional three lines of recommended treatment can be applied in most cases. These include oral therapy as the first line, local therapy as second and operative treatment as the third line.[50]

Integral to the discussion on ED treatment is an understanding of how EF is assessed. Although several validated questionnaires have been developed specifically to assess the EF after prostate cancer treatment, regular International Index of Erectile, Function (IIEF) test and its variation are possible and effective to use for a quick assessment both before and after treatment, due to their simplicity and familiarity to general care practitioners. IIEF-5, also named Sexual Health Inventory For Men (SHIM) is an abbreviated version of the IIEF consisting of 5 questions, which is easier to implement in the clinical setting than the full version of the IIEF.[51] Generally, a score > 21 is considered to represent a normal EF.

Given pathophysiology of ED, the treatment strategy aims to improve oxygenation of cavernosal tissue and prevent structural changes by providing better blood supply. Thus, it has been proposed that using pharmacological or mechanical treatment for ED before, during and after prostate cancer treatment will improve blood supply and prevent cavernosal fibrosis. This concept, also named as "penile rehabilitation" or "erectile function rehabilitation", has been developed to specifically treat ED following radical prostatectomy, but can be applied to other prostate cancer treatment approaches too. Despite this, no official definition or widely accepted treatment plan has been established.[45]

A variety of treatment regimens have been introduced as penile rehabilitation strategies using PDE5i. According to the American Urological Association (AUA) meta-analyses that compared several penile rehabilitation regimens, including PDE5i and placebo among men who had RP indicate no difference in rates of restored EF between groups. In addition, early administration of PDE5i does not improve later responses to these medications compared to early administration of placebo.

A new useful algorithm to care for sexual dysfunction following prostate cancer treatment was recently developed by Canadian men's sexual health experts and published in Canadian Urological Association journal in December 2018.[52] This algorithm was based on a complex approach, which may be tailored to the individual patient (and partner) presentation. The baseline recommendations for all patients are attempts to perform a regular sexual activity (at least once a week) and involve the sexual partner in the treatment process. The algorithm divides into three sections. The first section includes recommendations for using PDE5i, ICI, MUSE or VED. Choosing certain conservative options depends on the type of prostate cancer treatment received (radiation versus surgery with different levels of cavernous nerve sparing), followed by the desired level of invasiveness (a mechanical device, medication or intracavernous injection).[52] Surgical options including rigid or inflatable penile prosthesis, are recommended as the final treatment line. These are usually not recommended during the early post-surgical phases to allow for natural recovery.[50]

The second section of the algorithm provides treatment recommendations according to time: pre- or post-prostate cancer treatment and according to patient goals for erectile recovery (long term versus short term). The third section of the algorithm is based on providing patients with an expected erection recovery timeline. This is intended to help patients realize the real time of the recovery process. Thus, even using pharmaceutical mechanical tools for ED after RP, some early recovery of mild to moderate erection is expected within 4 months after the operation in less than 10% of patients.[52]

Conclusion

In conclusion, similar to common ED, management of post-prostate cancer treatment ED can be initiated by general physicians by starting oral therapy and referring the patient to the urologist in refractory cases for a second and third line therapy. In such model, general physicians, using the algorithm suggested by Canadian men's sexual health experts, can start the ''rehabilitation treatment'' and, given longstanding relationships with the patient they can provide an important therapeutic impact that eventually improves clinical results. □

References

1. Kretschmer A, Nitti V. Surgical treatment of male postprostatectomy incontinence: current concepts. *Eur Urol Focus* 2017;3(4-5):364-376.
2. Tienza A, Robles JE, Hevia M et al. Prevalence analysis of urinary incontinence after radical prostatectomy and influential preoperative factors in a single institution influential preoperative factors in a single institution. *Aging Male* 2018; 21(1):24-30.
3. Caremel R, Corcos J. Incontinence after radical prostatectomy: anything new in its management? *Can Urol Assoc J* 2014;8(5-6): 202-212.
4. Hosier GW, Tennankore KK, Himmelman JG, Gajewski J, Cox AR. Overactive bladder and storage lower urinary tract symptoms following radical prostatectomy. *Urology* 2016;94: 193-197.
5. Singla AK. Male incontinence: pathophysiology and management. *Indian J Urol* 2007;23(2):174-179.
6. Majoros A, Bach D, Keszthelyi A, Hamvas A, Romics I. Urinary incontinence and voiding dysfunction after radical retropubic prostatectomy (prospective urodynamic study). *Neurourol Urodyn* 2006;15(1):2-7.
7. Biers S, Sievert K, Thiruchelvam N. Overactive bladder syndrome and lower urinary tract symptoms after prostate cancer treatment. *Curr Opin Urol* 2017;27(3):307–313.
8. Leapman MS, Stone NN, Mock S, Stock RG, Hall SJ. Urinary incontinence following prostate brachytherapy. *Urology* 2016; 95:151-157.
9. Ferrer M, Guedea F, Suárez JF et al. Quality of life impact of treatments for localized prostate cancer: cohort study with a 5 year follow-up. *Radiother Oncol* 2013;108(2):306-313.
10. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. *BJU Int* 2012;109(11):1648-1654.
11. Uchida T, Tomonaga T, Kim H et al. Improved outcomes with advancements in high intensity focused ultrasound devices for the treatment of localized prostate cancer. *J Urol* 2015;193(1): | 103-110.
12. Liu YY, Chiang PH. Comparisons of oncological and functional outcomes between primary whole-gland cryoablation and high intensity focused ultrasound for localized prostate cancer. *Ann Surg Oncol* 2016;23(1):328-334.
13. Siegel AL. Pelvic floor muscle training in males: practical applications. *Urology* 2014;84(1):1-7.
14. Anderson CA, Omar MI, Campbell SE et al. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev* 2015;1:CD001843.
15. Fernandez RA, García-Hermoso A, Solera-Martinez M. Improvement of continence rate with pelvic floor muscle training post-prostatectomy: a meta-analysis of randomized controlled trials. *Urol Int* 2015;94(2):125-132.
16. Barnard J, Westenberg AM. The penile clamp: medieval pain or makeshift gain? *Neurourol Urodyn* 2015;34(2):116:115–116.
17. Kalra S, Srinivas PR, Manikandan R, Dorairajan LN. Urethral diverticulum: a potential hazard of penile clamp application for male urinary incontinence. *BMJ Case Rep* 2015;2015:bcr2015209957.
18. Ventimiglia B, Sigona M, Di Dio A, Puglisi T, Costantino G. Urinary incontinence and neuropathy after radical prostatectomy: diagnosis and treatment. *Urologia* 2015;82(1):42-45.
19. Løvvik A, Müller S, Patel HR. Pharmacological treatment of post-prostatectomy incontinence: what is the evidence? *Drugs Aging* 2016;33(8):535-544.
20. Bianco FJ, Albala DM, Belkoff LH et al. Placebo control, phase 4, multicenter study evaluating urinary continence after robotic assisted radical prostatectomy. *J Urol* 2015;193(4):1305-1310.
21. Malik RD, Cohn JA, Chung DE, Bales GT. Assessing variability of the 24-hour pad weight test in men with post-prostatectomy incontinence. *Int Braz J Urol* 2016;42(2):327-333.
22. Syan R, Nitti VW. Post-prostatectomy Incontinence Initial Evaluation. In: Sandhu J. (eds) Urinary Dysfunction in Prostate Cancer. Springer Cham. 2016
23. Chughtai B, Sedrakyan A, Isaacs AJ et al. National study of utilization of male incontinence procedures. *Neurourol Urodyn* 2016;35(1):74-80.
24. Miller AR, Linder BJ, Rangel LJ, Yang DY, Elliott DS. The impact of incontinence etiology on artificial urinary sphincter outcomes. *Investig Clin Urol* 2017;58(4):241-246.
25. Husch T, Kretschmer A, Thomsen F et al. Risk factors for failure of male slings and artificial urinary sphincters: results from a large middle European cohort study. *Urol Int* 2017;99(1):14-21.
26. Ravier E, Fassi-Fehri H, Crouzet S, Gelet A, Abid N, Martin X. Complications after artificial urinary sphincter implantation in patients with or without prior radiotherapy. *BJU Int* 2015;115(2):300-307.
27. Loh-Doyle JC, Hartman N, Nazemi A et al. (2018) Mechanical failure rates of artificial urinary sphincter components: is the 3.5-cm urethral cuff at higher risk? *Neurourol Urodyn* 2019;38(1):187-192.
28. Ostrowski I, Blewniewski M, Neugart F et al. Multicentre experience with ZSI 375 artificial urinary sphincter for the treatment of stress urinary incontinence in men. *Urologia* 2017;84(3):148-152.
29. Seweryn J, Bauer W, Ponholzer A, Schramek P. Initial experience and results with a new adjustable transobturator male system for the treatment of stress urinary incontinence. *J Urol* 2012;187(3):956-961.
30. Cornel EB. Argus-T adjustable male sling: the influence of surgical technique on complications and short-term efficacy. *Urol Int* 2016;96(2):164-170.
31. Friedl A, Muhistadt S, Zachoval R et al. Long-term outcome of the adjustable transobturator male system (ATOMS): results of a European multicentre study. *BJU Int* 2017;119(5):785-792.
32. Bauer RM, Grabbert MT, Klehr B et al. 36-month data for the AdVance XP ® male sling: results of a prospective multicentre study. *BJU Int* 119(4):626-630.
33. Chung E. Contemporary surgical devices for male stress urinary incontinence: a review of technological advances in current continence surgery. *Transl Androl Urol* 2017;6(Suppl2):S112–S121.
34. Rehder P, Gozzi C. Transobturator sling suspension for male urinary incontinence including post-radical prostatectomy. *Eur Urol* 2007;52(3):860-866.
35. Crivellaro S, Morlacco A, Bodo G et al. Systematic review of surgical treatment of post radical prostatectomy stress urinary incontinence. *Neurourol Urodyn* 2016;35(8):875-881.
36. Venturino L, Dalpiaz O, Pummer K, Primus G. Adjustable continence balloons in men: adjustments do not translate into long-term continence. *Urology* 2015;85(6):1448-1452.
37. Chung A, Lynch W, McCammon K. Outcomes of periurethral bulking agent injection for treatment of postprostatectomy. *Eur Urol Suppl* 2018;17(2):e1655.
38. Eastham JA, Scardino PT, Kattan MW. Predicting an optimal outcome after radical prostatectomy: the trifecta nomogram. *J Urol* 2008;179(6):2207-2211.
39. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: A meta-analysis. *J Sex Med* 2009;6(9):2538-2546.
40. Nelson CJ, Scardino PT, Eastham JA, Mulhall JP. Back to baseline: erectile function recovery after radical prostatectomy from the patients' perspective. *J Sex Med* 2013;10(6):1636-1643.
41. Capogrosso P, Vertosick EA, Benfante NE et al. Are we improving erectile function recovery after radical prostatectomy? Analysis of patients treated over the last decade. *Eur Urol* 2019;75(2):221-228.

42. Mahmood J, Shamah AA, Creed TM et al. Radiation-induced erectile dysfunction: Recent advances and future directions. *Adv Radiat Oncol* 2016;1(3):161-169.
43. Abdullah E, Idris A, Saparon A. Papr reduction using scs-slm technique in stfbc mimo-ofdm. *ARPN J Eng Appl Sci* 2017;12(10): 3218-3221.
44. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urol Clin North Am* 2005; 32(4):32:379-395.
45. Sopko NA, Burnett AL. Erection rehabilitation following prostatectomy-current strategies and future directions. *Nat Rev Urol* 2016;13(4):216-225.
46. Ramsay CR, Adewuyi TE, Gray J et al. Ablative therapy for people with localised prostate cancer: A systematic review and economic evaluation. *Health Technol Assess* 2015;19(49):1-490.
47. Postema AW, De Reijke TM, Ukimura O et al. Standardization of definitions in focal therapy of prostate cancer: report from a Delphi consensus project. *World J Urol* 2016;34(10):34:1373-1382.
48. Faure Walker NA, Norris JM, Shah TT et al. A comparison of time taken to return to baseline erectile function following focal and whole gland ablative therapies for localized prostate cancer: A systematic review. *Urol Oncol* 2018;36(2):67-76.
49. Li LY, Lin Z, Yang M, Gao X, Xia TL, Ding T. Comparison of penile size and erectile function after high-intensity focused ultrasound and targeted cryoablation for localized prostate cancer: a prospective pilot study. *J Sex Me*d 2010;7(9):3135-3142.
50. Bella AJ, Lee JC, Carrier S, Benard F, Brock GB. 2015 CUA Practice guidelines for erectile dysfunction. *Can Urol Assoc J* 2015;9(l-2)23-29.
51. Cappelleri JC, Rosen RC. The Sexual Health Inventory for Men (SHIM): A 5-year review of research and clinical experience. *Int J Impot Res* 2005;17(4):307-319.
52. Elterman DS, Petrella AR, Asseldonk B. Van et al. Canadian consensus algorithm for erectile rehabilitation following prostate cancer treatment. *Can Urol Assoc J* 2018; epub ahead of print.