Future Directions in urology Symposium

FDUS 2018 Consensus Statements

The 19th Annual Future Directions in Urology Symposium: Directions for the Next Generation of Treatments

August 11-14, 2018

PROGRAM DIRECTOR
E. David Crawford, MD
University of Colorado, Denver
Aurora, CO

Grand Rounds in UROLOGY

Presented by Grand Rounds in Urology

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ABOUT GRAND ROUNDS IN UROLOGY

The mission of *Grand Rounds in Urology (GRU)* is to bring together a network of urology professionals, both online and in live meetings, to spread best practice knowledge through lectures, conversations, information sharing, and constructive debates, ultimately improving physician performance and patient outcomes throughout the world.

***GRU* accomplishes its mission in the following ways:**

1. **Live Meetings:** *GRU* is an organizer and host of international conferences and symposia that bring together the top thought leaders in the treatment of urologic disease. Our meetings focus on current best treatment practices, as well as future trends and directions. These educational programs offer highly interactive dialog with state-of-the-art presentations.

2. **Valuable Information and Online Learning Products:** Virtual Grand Rounds, Platinum Lecture Series, Ask the Expert, as well as presentations from international meetings provide the resources urologists need to stay informed. Online courses, CME and non-CME, provide urologists with the best practices for treating patients.

3. **Networking:** *GRU* serves to constantly connect professional learners, faculty experts, and industry partners through its live and virtual activities. These opportunities facilitate high-level collaborations to evolve best practices in urologic care.

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This meeting was started 20 years ago to evaluate where we are and plan where we should be in 5 to 10 years in a number of urologic disease states.

The meeting brings together experts in the field not only urologists but also medical oncologists, radiation oncologists,radiologists, family practice as well as researchers and industry leaders to review current trends and prospects.

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INTRODUCTION

Future Directions in urology Symposium

The 19th Annual Future Directions in Urology Symposium: Directions for the Next Generation of Treatments

During The 19th Annual Future Directions in Urology Symposium (FDUS), a think-tank of Key Opinion Leaders in the treatment of urologic disease completed the following consensus statements.

SESSION 1:

Next Generation Developments in Bladder Cancer

Session Moderators:
Michael S. Cookson, MD and Sam S. Chang, MD, MBA

Michael S. Cookson, MD
University of Oklahoma
Oklahoma City, OK

Sam S. Chang, MD, MBA
Vanderbilt University
Nashville, TN

1. We need to develop a consensus on standard testing for immunotherapy and molecular therapy testing to facilitate eligibility for immuno-oncology and molecular therapy.

2. Identifying predictive PD-1/PD-L1 expression markers for patients with metastatic and possibly non-metastatic disease is necessary.

3. We should incorporate molecular diagnostics into the risk stratification of bladder cancer.

4. Improving the diagnostic accuracy, evaluation, and risk stratification of noninvasive bladder cancers by better determining tissue, radiographic, and molecular predictors of disease risk needs to be emphasized.

5. We should more clearly risk-stratify T1 tumors to assist clinicians in clinical management and to identify those patients eligible for future clinical trials.

6. In patients with T2-4 urothelial carcinoma (UCC), the risk/benefit of T0 after transurethral resection (TUR) prior to and following neoadjuvant chemotherapy (NAC) should be further explored.

7. The beneficial impact of systemic immunotherapy or combination therapy for high-risk noninvasive bladder cancers needs to be studied.

5-Year Predictions:

1. Transurethral resection of bladder tumor (TURBT) will be done in the same way.
2. No consensus urine marker will exist yet.
3. Molecular profiling of invasive and non-invasive tumors will be more commonplace and will help determine therapeutic choices.
4. Bladder sparing multimodality will become more commonly chosen for invasive disease.

SESSION 2:

Next Generation Developments in GU Cancer

Session Moderator:
Daniel P. Petrylak, MD

Daniel P. Petrylak, MD
Yale Cancer Center
New Haven, CT

1. Trials ongoing for adjuvant therapy in high-risk renal cancer, with current tyrosine-kinase inhibitors (TKIs), are investigating only progression-free survival (PFS) as primary endpoint. We think overall survival (OS) is a more important indicator of outcome. The group questioned the clinical significance of an improvement in PFS with significant toxicity, without a benefit in survival. Quality of life changes become more relevant especially in a patient who starts treatment without symptoms. This is particularly important in light of the known toxicities of tyrosine kinase inhibitors in this setting.

2. The CARMENA trial found, in intermediate to high risk patients with metastatic disease, that patients treated with nephrectomy followed by sunitinib had an inferior survival than patients undergoing treatment with sunitinib alone. The group agreed that more studies are needed to evaluate nephrectomy several patient groups 1) low-risk metastatic renal patients undergoing either TKI or immune therapy and 2) Intermidiate/high risk patient metastatic patients undergoing immune therapy.

3. Neoadjuvant trials are currently being performed with immunotherapy alone or the combination of immunotherapy with targeted therapies. The optimal combination and timing in relationship to surgery are yet to be defined. Is the neoadjuvant approach better than that adjuvant approach? Does neoadjuvant therapy proved a constant source of antigen exposure for immune therapy, and thus have an advantage over adjuvant therapy?

4. The role of biomarkers, particularly PDL-1 status needs to be better defined. Is PDL 1 expression predictive of response or prognostic for survival, or both? Can this marker be used to design neoadjuvant/adjuvant trials.

5-Year Predictions:

1. Combination antiangiogensis therapy/checkpoint inhibition therapy will be a standard of care for metastatic disease.
2. Neoadjuvant/adjuvant immune therapy trials will be completed.

SESSION 3:

Next Generation General Urology and Men's Health

Session Moderator:
Mohit Khera, MD, MBA, MPH

Mohit Khera, MD, MBA, MPH
Baylor College of Medicine
Houston, TX

1. Guidelines among involved societies need to be reconciled to identify which men should be treated, as well as how and when they should be monitored.

   Both the American Urological Association (AUA) guidelines and Endocrine Society (Endo) guidelines state that hypogonadal men should be treated with testosterone only when they have a low serum testosterone (T) and hypogonadal symptoms.

   AUA: ***"The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs"***

   Endo: ***"We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated)"***

   Our recommended monitoring schedule is every 6-12 months with testosterone, PSA, and hematocrit levels.

   The AUA guidelines should also state that, ***"Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer."***

   The Endo guidelines slightly differ, stating, ***"Many older men harbor small foci of subclinical cancer in their prostate; we do not know whether T replacement might cause these subclinical cancers to grow and become clinically overt."***

   We find the AUA guidelines to be more acceptable when it comes to prostate cancer and testosterone, so the AUA statement on prostate cancer and testosterone should be followed.

2. We need to verify the safety of T replacement in men with lower urinary tract symptom (LUTS) due to benign prostatic hyperplasia (BPH).

   The largest meta-analysis assessing T and LUTS/BPH is by DeLay and Kohler (2016). This meta-analysis demonstrates that every study observing this topic either found no increase in LUTS or BPH symptoms or no effect at all after testosterone replacement therapy (TRT). Thus, there is no convincing data to support that T causes worsening on BPH/LUTS symptoms.

The AUA guidelines have no statement on BPH and T. The Endo guidelines state the following: ***"T therapy does not worsen lower urinary tract symptoms (LUTS) in men who do not have severe LUTS prior to treatment," as well as, "We do not know whether T worsens LUTS in men who have severe LUTS at baseline, because such men have been excluded from T trials."***

TRT has not been shown to worsen LUTS in men with mild to moderate BPH. More studies are needed to assess the effects of TRT in men with severe LUTS.

3. We need to establish the safety of T replacement in men on active surveillance for small volume prostate cancer.

   There are only three retrospective studies in the literature, so we assert the following consensus statement: ***Patients with testosterone deficiency and on Active Surveillance for small volume prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy.***

4. We need to establish the safety of T replacement in men with treated prostate cancer.

   When it comes to giving men T after prostate cancer treatment (i.e., radical prostatectomy), both AUA and Endo guidelines are similar in that they state more studies need to be done, and this should be done with caution.

   AUA: ***"Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy."***

   Endo: ***"Although some clinicians have suggested considering patients with a history of organ-confined prostate cancer for T replacement on an individualized basis—if they have undergone radical prostatectomy, have undetectable PSA, and no detectable residual disease 2 or more years after surgery —the lack of data from RCTs precludes a general recommendation."***

   For this topic, we suggest adopting the AUA guidelines with the addition that retrospective and case controlled studies thus far have not demonstrated increased prostate cancer recurrence when giving men testosterone after prostate cancer therapy.

5. Physicians must choose the best method of T administration, out of injection, gels, or creams. The best method is patient specific. These factors are as follows:

   a. **Cost** – Insurance now often dictates what we can prescribe.
   b. **Compliance** – If patients cannot remember to put on a gel every day, we move to injections or pellets.
   c. **Concentration** – If one gel or formulation is not able to achieve T levels in the normal range, we switch to another formulation.
   d. **Convenience** – Some patients prefer long acting as opposed to short acting gels.

As a final consideration, the risk of transference is an important safety concern to include in deciding the best method of administering testosterone. If the patient has a young child or pregnant wife, the patient should not receive gels to avoid risk of transference.

6. We believe the treatment of nocturia should follow currently published BPH guidelines for workup. Consideration of newer formulation when contraindications to antidiuretic hormone (ADH) is eliminated and other interventions are not optimal.

7. The guidelines for T replacement in men with hypogonadism, with or without concomitant LUTS due to BPH and/or small volume prostate cancer, need to clarify the frequency of monitoring of T and PSA levels. Studies to determine the safety of T replacement in hypogonadal men with LUTS due to BPH and who are known to harbor small volume prostate cancer that is under active surveillance are necessary.

Five-Year Predictions:

1. Testosterone will be used to help improve BPH/LUTS symptoms as it is a strong anti-inflammatory in the prostate.
2. A large, randomized, placebo-controlled study will be conducted to assess the risk of prostate cancer following TRT.
3. TRT will be more frequently used in patients with metastatic prostate cancer as a form of therapy.

SESSION 4:

Next Generation in Biomarkers

Session Moderator:
M. Scott Lucia, MD

M. Scott Lucia, MD
University of Colorado, Denver
Aurora, CO

1. More than 25 years of PSA testing has shown us its limitations. To move forward, we need to incorporate imaging (i.e. mpMRI, PET, HFUS) and biomarkers to enhance detection of curable, significant prostate cancer.

2. Novel precision targets have been identified in prostate cancer through genomic sequencing efforts of both tumor and germline DNA, including many mutations that may be actionable in screening and/or therapy, and many that may have implications for unaffected family members. Efforts to streamline and standardize deep sequencing protocols with uniform reporting, reduce turn-around times, and reduce costs are critical for moving forward.

3. Caregivers should give more effort towards obtaining detailed family histories in prostate cancer patients. Critical cancers that need to documented beyond prostate include the following cancers: breast, ovarian, pancreatic, melanoma, and Lynch Syndrome.

4. Improving the diagnostic accuracy, evaluation, and risk stratification of bladder cancers by better determining tissue, radiographic, and molecular predictors of disease risk needs to be emphasized.

5. DNA repair alterations are reasonably common and worth testing for in metastatic prostate cancer and considering for high risk localized prostate cancer. There are many pitfalls to testing, and it is important to ensure that bi-allelic loss occurs when a gene presents on a report.

   Overall, informatics and data management is a concern for utilizing biomarkers in GU cancers. We find there is a need for long-term local ownership and management of genetic findings to lead to the establishment of a standard of care regarding genetic testing.

SESSION 5:

Next Generation Imaging in Localized Prostate Cancer

Session Moderator:
Phillip J. Koo, MD

Phillip J. Koo, MD
Banner MD Anderson Cancer Center
Phoenix, AZ

1. Hydrogel spacing is rapidly becoming standard of care for prostate cancer radiotherapy with growing adoption by the urology community.

2. Hydrogel technology may be applied to other organs throughout the body that could benefit from marking or space creation (i.e. bladder, gynecological, and pancreatic cancers).

3. Opportunities exist for clinical investigation of adjacent prostate indications (i.e. post prostatectomy, ablative therapies).

4. Prostate MRI continues to serve an important role in the evaluation of primary disease. Clinical trial data such as PRECISION and PROMIS continue to emerge that will solidify and expand the use of prostate MRI. Standardization and variability of prostate MRI remains problematic and will hopefully improve with increased adoption of PI-RADS Version 2.

5. Preliminary evidence regarding the use of PET/CT for the characterization of primary prostate cancer is promising however clinical trial data is necessary to prove the performance and clinical utility of the tool in the management of prostate cancer patients.

SESSION 6:

Next Generation Therapeutic Layering and Sequencing

Session Moderator:
Leonard Gomella, MD, FACS

Leonard G. Gomella, MD, FACS
Thomas Jefferson University
Philadelphia, PA

1. The current status of health care economics is unsustainable for the nation and a transition to value-based care is both desirable and inevitable. During this transition, it is imperative that we as urologists remain actively engaged with regulatory and legislative bodies to both educate ourselves and advocate for our patients so that the resources necessary to diagnose, treat, and research new therapies for patients with genitourinary disease are appropriately allocated.

2. We need to continue to find ways to utilize advanced practice providers (APPs) and provide a team-based approach to urological care, especially to extend access to care and improve efficiency.

3. Next Generation Imaging (NGI) using positron-emission tomography (PET) for the detection of metastatic disease undoubtedly performs better than conventional imaging. Future directions need to focus on multidisciplinary investigation of the impact on outcomes in order to identify the appropriate test in a specific clinical situation that will lead to the greatest clinical value.

4. Future clinical studies should strive to incorporate advanced image and data analytic tools in various clinical settings, including treatment response.

5. Therapeutic radiopharmaceuticals, such as radium-223 and prostate-specific membrane antigen (PSMA) targeted agents, will serve an important role in the treatment of advanced prostate cancer patients.

SESSION 7:

Next Generation Advanced and Castration-Resistant Prostate Cancer

Session Moderator:
Evan Y. Yu, MD

Evan Y. Yu, MD
University of Washington
Seattle, WA

1. The new standard for PSA testosterone nadir should be redefined to a lower level in light of newer laboratory measurements.

2. Immunotherapy with sipuleucel-T is more efficacious with lower disease burden or, in other words, in patients with lower PSA. This therapy has clearly demonstrated a survival benefit. Other immunotherapies may have a benefit, but need to be studied further. We need biomarkers to aid in selecting patients for immunotherapies.

3. New generation anti-androgens are well-tolerated with excellent oncologic outcomes. Choice of agents should be based on patient medical history.

4. Nonmetastatic castration-resistant (M0) disease should be treated after careful evaluation and discussion with the patients. Education of the definition of M0 disease should be actively pursued.

5. DNA repair alterations are reasonably common and may predispose to agents like poly adenosine diphosphate-ribose polymerase (PARP) inhibitors and double strand DNA break inducing drugs like platinum/radium-223. There may even be a role in unselected populations with PARP inhibitors given the abiraterone plus olaparib data, but data is not mature enough to confirm this.

6. Other ways to induce BRCAness, such as hypoxia and next generation antiandrogen therapy, need to be evaluated in trials.

7. Newer PD-1 and PD-L1 antibodies may have a role in advanced prostate cancer patients, certainly for those with microsatellite instability, but there are many other patient populations and combinations ongoing.

8. There is a strong role for novel AR targeted therapies—abiraterone for metastatic hormone sensitive prostate cancer as well as apalutamide or enzalutamide for M0 castration resistant prostate cancer—earlier in the treatment paradigm.

9. Radiographic Assessments for Detection of Advanced Recurrence (RADAR) guidelines can be an important foundation for building clinical treatment decisions in advanced prostate cancer.

   Overall, we believe every patient with CRPC deserves to have all appropriate agents available during the course of their disease.

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