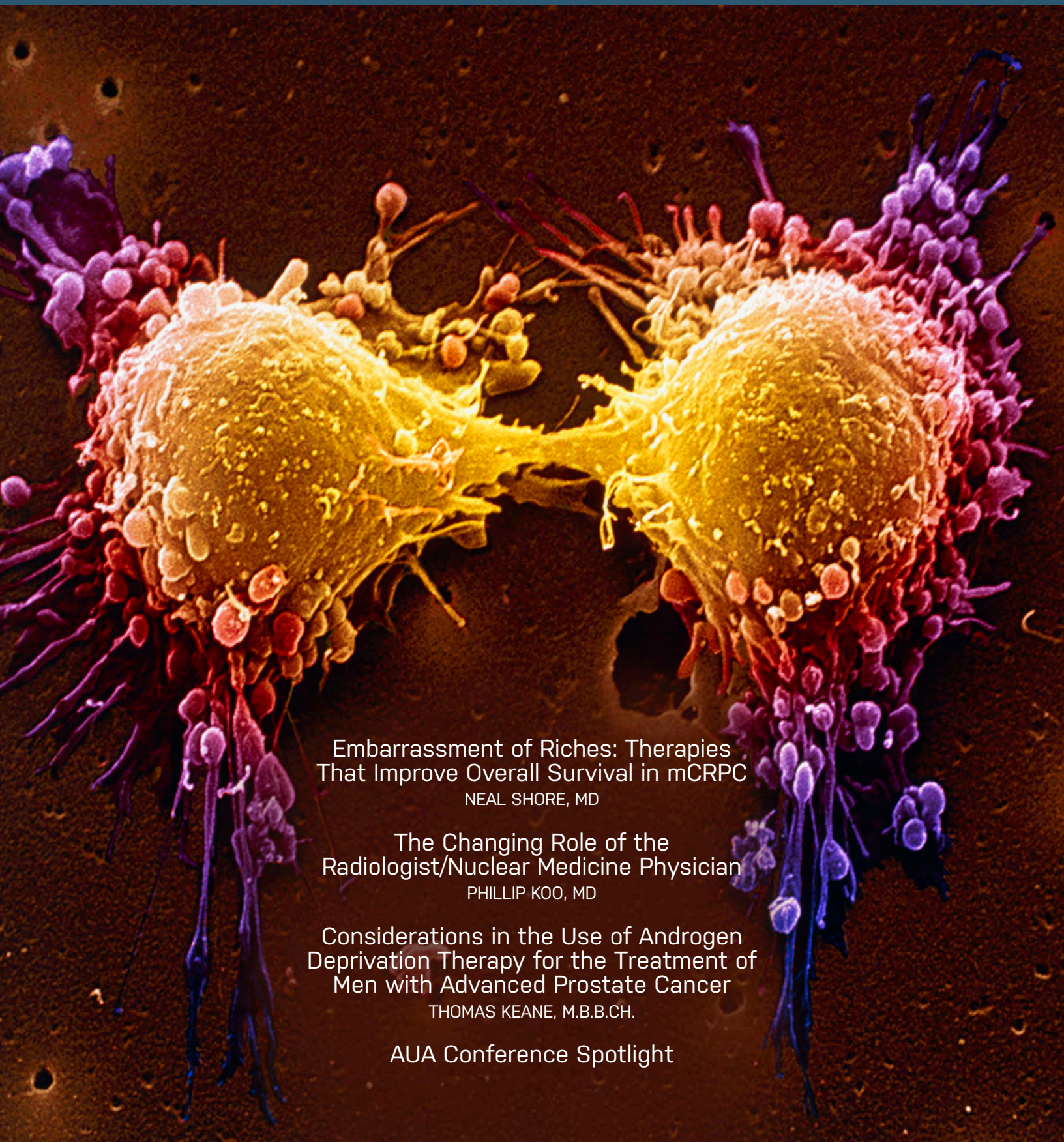
EVERYDAY UROLOGY

ONCOLOGY INSIGHTS: A UROTODAY PUBLICATION

VOLUME 1, ISSUE 1



Embarrassment of Riches: Therapies That Improve Overall Survival in mCRPC

NEAL SHORE, MD

The Changing Role of the Radiologist/Nuclear Medicine Physician

PHILLIP KOO, MD

Considerations in the Use of Androgen Deprivation Therapy for the Treatment of Men with Advanced Prostate Cancer

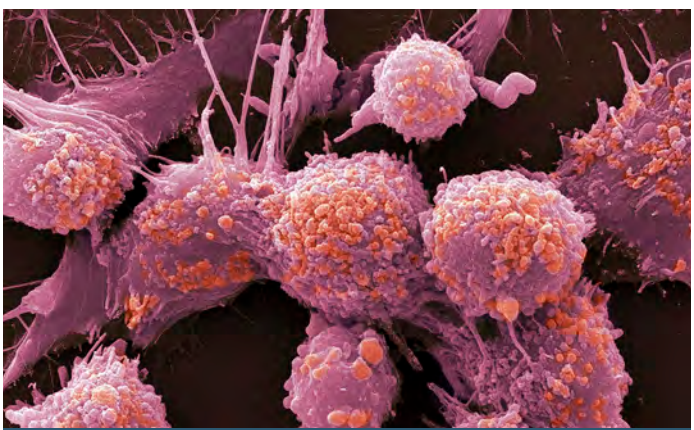
THOMAS KEANE, M.B.B.CH.

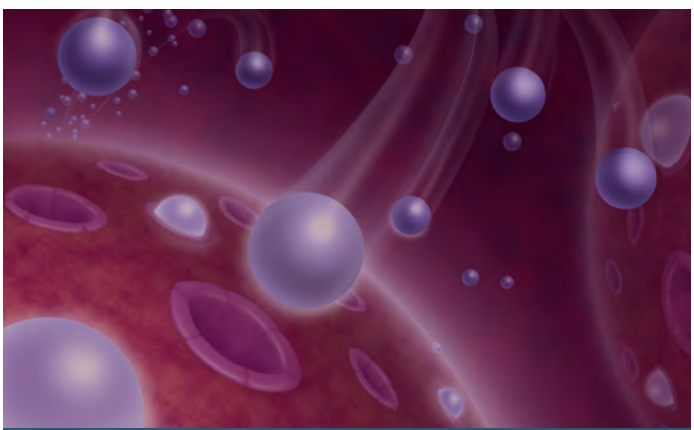
AUA Conference Spotlight

EVERYDAY UROLOGY

ONCOLOGY INSIGHTS: A UROTODAY PUBLICATION VOLUME 1, ISSUE 1

Contents





AUA SPOTLIGHT

DIGITAL SCIENCE PRESS

About Digital Science Press

Digital Science Press, Inc, has been publishing UroToday.com since 2003 and has developed OncToday.com, in 2016. Digital Science Press is committed to providing factually accurate, timely, evidence-based urological and oncology information to healthcare providers around the globe. In 2003 we recognized that there are a significant number of scientific publications and medical conferences and yet there was no single, easy to access platform that accommodates this content. UroToday.com became the reference platform that aggregates the relevant, unbiased urology disease and treatment-based content and is committed to assisting healthcare professionals in staying up-to-date.

Everyday Urology™
ONCOLOGY INSIGHTS: A UROTODAY PUBLICATION

Everyday Urology™- Oncology Insights™ (ISSN 2473-3784) is published four times a year by Digital Science Press, Inc., business office located at 11448 Deerfield Drive, Suite 2, Truckee, CA. 96161.

POSTMASTER: Send address changes to *Everyday Urology™- Oncology Insights™* Digital Science Press, Inc. Subscription Customer Service, 11448 Deerfield Drive, Suite 2, Truckee, CA 96161

CUSTOMER SERVICE: Customer service Inquiries should be sent to publisher@urotoday.com Subscription inquiries should be sent to: cleonard@urotoday.com Access to this journal is online at www.urotoday.com Other correspondence for Digital Science Press, Inc. should be sent to: Attention: Digital Science Press, Inc. 11448 Deerfield Drive, Suite 2 Truckee, CA 96161

FROM THE DESK OF THE EDITOR

Welcome to the inaugural issue of *Everyday Urology-Oncology Insights*, brought to you by Digital Science Press, Inc, publishers of UroToday.com. For the past 13 years, UroToday has demonstrated its commitment to providing accurate, timely, evidence-based urology and oncology information to the global community of health-care providers. With its inception in 2003, there was a recognition that there are a multitude of ongoing scientific publications and medical conferences; nevertheless, an easy to access daily platform to acknowledge, report and accommodates this content did not exist. UroToday.com initiated its web based platform to succinctly aggregate the contemporaneous and most relevant urology content on a real time, daily basis in order to allow busy clinicians to remain up to date with the newest research, approvals, and meeting information.

The inaugural issue of *Everyday Urology-Oncology Insights* focuses on the ever evolving treatment of advanced prostate cancer. It highlights the multidisciplinary approach for optimally treating the advanced prostate cancer patient. The print publication will provide a visually driven format with original articles, thus providing the benefit of a tactile experience and the unique features for hand held reading. This publication will broaden the constituency of our current digital presence by specifically selecting GU clinicians: inclusive of GU Oncologists (Urologists and Medical Oncologists), Radiation Oncologists and Nuclear medicine physicians within the United States.

I am honored to be *Everyday Urology's* physician editor in chief and have authored our cover story, *''Embarrassment of Riches: Therapies that improve Overall Survival in Patient with mCRPC.''* Here I will describe the emerging treatment options for our advanced prostate cancer patients, and their life prolonging benefits. This month's Expert Perspective, is written by Phillip Koo, MD, titled *''The Changing Role of the Radiologist/Nuclear Medicine Physician in the Management of Advanced Prostate Cancer Patients''*. Dr. Koo will describe his process for developing a successful, multidisciplinary relationship for the maximal benefit of advanced prostate cancer care. Our feature article will discuss, *''Considerations in the Use of Androgen Deprivation Therapy for the treatment of men with advanced prostate cancer''*, with an interview with Dr. Thomas Keane, reviewing what is known regarding ADT, and more importantly, the controversial and often debated unmet needs for administration, monitoring, and utilization of androgen deprivation.

As the publication evolves, we assuredly welcome your suggestions and feedback, and sincerely invite you to contribute your own articles and commentary.

Thank you for reading, *Everyday Urology-Oncology Insights*.

NEAL SHORE, MD

Neal Shore, MD *is an internationally recognized expert in systemic therapies for patients with advanced urologic cancers and innovative therapies to treat patients suffering from prostate enlargement symptoms. Dr. Shore was recently appointed President-Elect of the Large Urology Group Practice Association (LUGPA), which seeks to provide urologists with all the tools they need to effectively care for patients. Neal D. Shore, MD, FACS, is the Medical Director of the Carolina Urologic Research Center. He practices with Atlantic Urology Clinics in Myrtle Beach, South Carolina. Dr. Shore has conducted more than 100 clinical trials, focusing mainly on prostate and bladder disease.*

MESSAGE FROM THE FOUNDER

Welcome readers to the first issue of *Everyday Urology-Oncology Insights*. I am excited that you have taken the leap to print and appreciate your support on this journey. I have had the privilege to work with many of you through advisory boards, lecture recordings and content development or spent time together at countless AUA and ASCO conferences, and shared in learning from your presentations and research. If this is your first experience with Digital Science Press Inc, you are joining a strong community of over 20,000 users worldwide!

I founded Digital Press Inc. and UroToday.com in 2003 with the same passion that I have now, to provide quality, state of the art education with the goal to improve access to the data towards improving patient outcomes. UroToday's digital publication has remained adaptable, as new technologies have allowed for the instantaneous communication of the most relevant content globally UroToday posts daily, approximately 250 separate educational items per week, with more than 120,000 live webpages.

In 2015 this digital-first company recognized the value in providing a quarterly print publication, comprising original articles and commentaries as well as reporting highlights and cutting edge information from worldwide meetings and congresses.

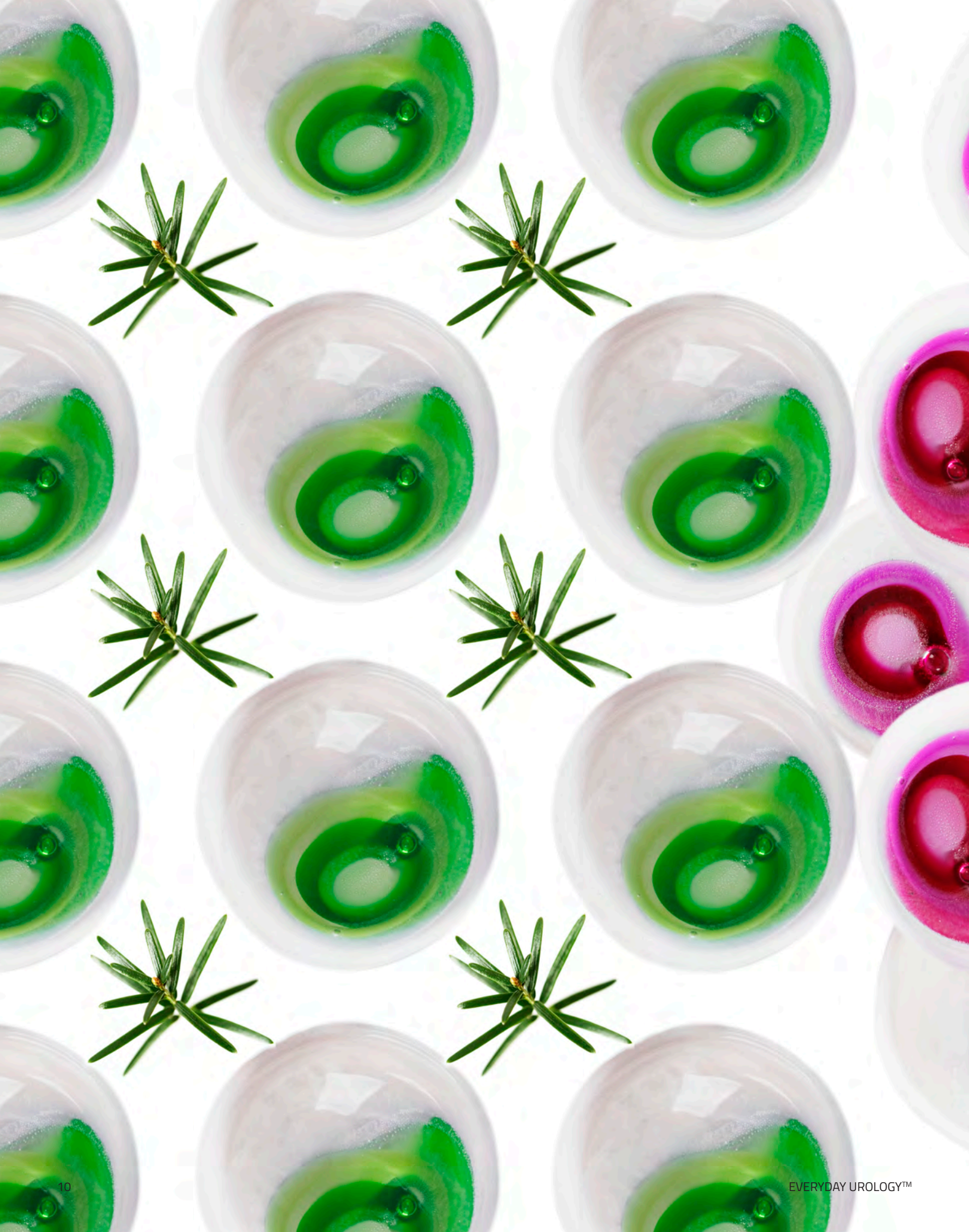
Everyday Urology's goal is to provide the same quality content we have been providing for over a decade but taking a deeper look into the evolving practice of urological cancer treatment by reaching a multi-disciplinary audience of academics, medical oncologists, urologists as well as radiation oncologists and radiologists, with guest contributors across all of these specialties from some of the best hospitals and practices in the country.

I would like to thank our editor in chief, Neal Shore and other contributors that have been instrumental in shaping the look and feel of the publication; Philip Koo, Thomas Keane and Bishoy Faltas. I hope you enjoy the first issue and I welcome your comments, feedback and ideas to further evolve and improve *Everyday Urology-Oncology Insights*.

Thank you for your continued support.

GINA B. CARITHERS

Gina B. Carithers *is the founder of UroToday, the UroToday International Journal and recently OncToday all Digital Science Press publications. With over 20 years at DuPont Pharmaceuticals, Ms. Carithers acquired a diversified experience in global commercialization and marketing and a passion for providing quality, state of the art access to unbiased information that translates clinical trial data into improving health and patient outcomes.*



EMBARRASSMENT OF RICHES:

Therapies that Improve Overall Survival in mCRPC

By Neal Shore, MD

Before 2004, there was an unmet need for survival prolonging therapies in men with castration-resistant prostate cancer (CRPC). Palliative therapeutic options were the standard of care. As a result, there was a pervasive nihilism regarding the therapeutic management of men with advanced prostate cancer, especially after they ceased responding to androgen suppressive therapy.

In 2016, the situation is far different. In 2004, the first medication to improve survival rates in patients with CRPC was approved: chemotherapy with docetaxel, which clearly demonstrated an overall survival benefit compared with mitoxantrone therapy. Since 2010, five new therapies have also been added to the armamentarium, including the immunotherapy, sipuleucel-T; the novel hormonal antiandrogen therapies, abiraterone and enzalutamide; the chemotherapy, cabazitaxel and the radionuclide therapy, radium-223.

Some have now stated that we have an embarrassment of riches when it comes to the treatment of metastatic CRPC. Yet, there are ongoing and significant questions and concerns that remain for urologists, medical oncologists, and radiation oncologists: How do we select the right therapy for the right patient at the right time, while being mindful of therapeutic effect, toxicities, and cost? How can we optimally combine and sequence these treatments? Fortunately, there are many phase II and phase III clinical trials attempting to fortify the evidenced based literature in order to answer these unmet needs.

First, let's consider a review of the different medications approved and accessible for the treatment of metastatic CRPC.

Docetaxel was approved by the FDA as first-line therapy for advanced CRPC based on phase III clinical trials that showed that this taxane based chemotherapy extended survival by a median of 2.4- 2.9 months over mitoxantrone.[1] Numerous, subsequent clinical trials have studied the addition of other unique mechanism of action therapies to docetaxel—with the primary goal of improving docetaxel monotherapy survival rates. Unfortunately, none of these trials have succeeded, and thus we still lack data to support a combination docetaxel regimen for attaining a survival benefit.

Sipuleucel-T, an autologous cellular vaccine, was approved by the FDA in 2010 for metastatic CRPC on the strength of phase III clinical trial data that showed a median overall survival rate of 25.8 months for sipuleucel-T vs. 21.7 months versus the placebo arm. The trial demonstrated a 22% reduction in mortality risk, and it was the first immunotherapy to demonstrate a survival benefit for any solid tumor malignancy. Currently, the United States is the only country to have both regulatory and commercial approval for sipuleucel-T . Sipuleucel-T is manufactured by combining a fusion protein with the individual patient's leukapharesis obtain dendritic cell population, and ultimately delivered by infusion 2 to 3 days later, whereby 3 doses, each given as 60-minute IV infusions, 2 weeks apart, which completes the course of therapy. The safety and tolerability for administration of sipuleucel-T is well documented, and essentially, very well tolerated; e infusion reactions may occur, which can cause fever, myalgia, and hypotension.[2]

The novel hormonal therapy, abiraterone, an oral medication, is approved for the treatment of metastatic CRPC in combination with prednisone. In phase III trials it increased overall survival a median of 3.9 months compared versus placebo when administered post-docetaxel therapy. In chemotherapy-naïve patients, the medication improved survival by a median of 4.4 months compared with placebo.[3, 4] Abiraterone should be used with caution in patients with a history of significant congestive heart failure. The effects of abiraterone exposure may increase up to 10-fold when taken with meals, thus patients are instructed to ingest the medication in a non-fed state. Of note, recent trials are investigating its use with once daily 5mg prednisone and, even no prednisone use, for some patients. Because it can affect CYP enzymes, it's important to check drug-drug interactions. Before and during treatment, it's important to monitor blood pressure, signs of fluid retention, as well as electrolyte and hepatic function stability. If liver function tests are abnormal, drug dosing can be modified, interrupted with ongoing monitoring to allow for optimal dosing.

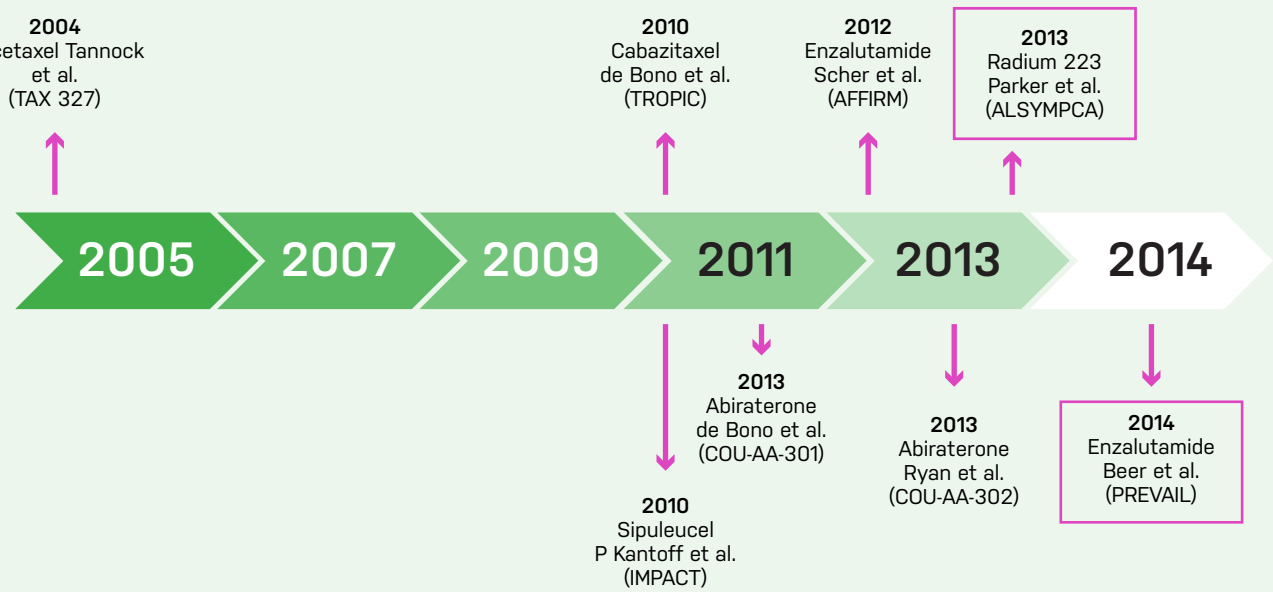
Enzalutamide, another novel hormonal CRPC agent, is also administered as an oral agent, but without a prednisone requirement. It was approved based upon randomized controlled trials that showed it extended survival a median of 4.8 months compared with placebo in patients who had previously received docetaxel. In a final phase III analysis, it also extended survival a median of 3.9 months in chemotherapy-naïve patients when compared with placebo. Of note, unique adverse events of interest, albeit in a very low percentage of patients, may precipitate seizures and fatigue. Similarly, enzalutamide is predominantly metabolized by the liver, and clinicians should be aware of certain listed drug-drug interactions. The current capsules may be ingested with or without food.[5, 6]

Cabazitaxel is another taxane based chemotherapy drug administered in combination with prednisone in patients with metastatic CRPC previously treated with docetaxel, whom have demonstrated progression. In clinical trials, cabazitaxel increased median survival by 2.4 months when compared with mitoxantrone/P. Similar to docetaxel, it is administered as a 1-hour infusion every 3 weeks with concomitant steroid use. As with other taxane based therapy, the primary safety considerations are myelosuppression. Both renal and hepatic impairment can provide further obstacle to the use of cabazitaxel. Many have noted the advantage of its use, compared to docetaxel, in observing less neuropathy, alopecia, and fatigue.[7]

The most recent CRPC approved therapy, radium-223, is indicated in the treatment of patients with metastatic CRPC with symptomatic bone metastases, but no known visceral metastatic disease. In the phase III ALSYMPCA clinical trial, it extended survival rates a median of 3.6 months for a trial population inclusive of both pre- and post-docetaxel CRPC patients. The ALSYMPCA trial enrolled patients with progressive CRPC with 2 or more bone metastases. A total of 921 patients were randomly assigned to receive radium-223 or a saline placebo infusion every 4 weeks for 6 cycles. The primary endpoint indicated that radium-223 treatment resulted in a 30% reduction in mortality. The medication

mCRPC Treatment Landscape

While the greater availability of treatment agents benefits patients, the multiple options and sequencing of medications complicates clinical decision-making.



also significantly prolonged median time to first symptomatic skeletal event.[8]

Additionally, radium-223 had a beneficial effect on delaying pain and also preserved health-related quality of life. The median time to initial opioid use was significantly longer for radium-223 than placebo (HR =.62), for instance. A higher percentage of patients in the radium-223 group than those in the placebo group had a clinically meaningful improvement in health-related quality of life as measured by the Functional Assessment of Cancer Therapy-Prostate score (an increase of 10 or more points above baseline during the drug administration period). Of the patients in the radium-223 group, 25% had significantly improved quality of life vs. 16% of those in the placebo group (p =.02).

In a small percentage of patients, radium-223 can cause grade 3-4 anemia, thrombocytopenia and neutropenia. Blood counts should be obtained prior to treatment initiation and before every dose in patients receiving radium-223, and those with compromised bone marrow reserve should be closely monitored.

Although there is a paucity of comparative data on these medications, guidelines by the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) provide us with guidance on which therapies are supported by level 1 evidence in sub types of patients with CRPC. Treatment of non-metastatic or M0 CRPC is clearly an unmet need, however, as none of the abovementioned CRPC therapies are approved for use in this setting. The best choices in these patients, therefore, are second-line hormonal therapies after an initial hormonal therapy failure, or preferably, a clinical trial. Patients should also be subject to close observation and follow-up with imaging when PSA levels increase 2 ng/mL or more, when PSA rises to 5 ng/mL and at every doubling of PSA level thereafter (based on PSA testing every 3 months).[9]

The second-line hormonal therapies in these patients include first-generation antiandrogens such as flutamide, bicalutamide and nilutamide, first generation androgen synthesis inhibitors (ketoconazole plus a steroid), or estrogens.

The guidelines suggest that patients with metastatic asymptomatic CRPC or those with minimal symptoms can benefit from abiraterone, enzalutamide and sipuleucel-T. Sipuleucel-T is ideally suited to be the first option in these patients, because

their immune systems may be less suppressed than those of patients with more extensive disease and tumor burden and thus may have a more robust response to the vaccine. In patients with metastatic CRPC with symptoms who are chemotherapy-naïve, docetaxel, radium-223, abiraterone and enzalutamide are also options. In patients who have already received docetaxel, all of these agents can be used in addition to sipuleucel-T and cabazitaxel.

The novel hormonal therapies, abiraterone and enzalutamide are particularly beneficial in patients with metastatic CRPC who are naïve to any therapy. Research and clinical experience indicate that many patients will experience a substantial decline in PSA with these agents, while perhaps 8% to 12% of those treated demonstrate primary resistance. Sensitivity to these medications may vary from patient to patient, and patients who are resistant to one agent may respond to the second, but usually for a limited duration.

PSA responses to the novel hormonal therapies can also vary depending on mutational predominance. Of note, patients who have the AR-V7 biomarker are unlikely to respond to either enzalutamide or abiraterone. However, patients with AR-V7 variants do respond to other therapies. Studies show that upwards of 50% of patients with CRPC who have this variant will respond to docetaxel or cabazitaxel.

Radium-223, with its unique proposed mechanism of action, enhancing apoptotic effect at bone mineralization sites, suggests its suitability fro combination therapy with the novel hormonal agents, specifically CRPC pts with bone metastases. It can be administered in patients with a wide spectrum of bone symptomology, and whether or not the patient has had previous chemotherapy. Unlike prior radiopharmaceuticals, it is not prescribed primarily for pain palliation, instead, should be prescribed for its overall survival benefits. Radium-223 can be given before or after chemotherapy, but not concomitantly with chemotherapy.[10]

As noted earlier, there is a paucity of data on combining or sequencing these approved CRPC agents, hence, treatment decisions in the clinic often depend on drug availability, performance status, age, patient comorbidities and the patient's response and resistance to prior therapies. The burden and location of disease, the pace of progression of the patient's cancer, whether the progression is systemic or focal, and patient preference also play a part in the decision-making process. It's essential to have a broad based and thoughtful discussion with the patient and caregivers about the advantages and disadvantages of all therapies.

Fortunately, there are many ongoing clinical trials are now testing the combination and sequencing of the new therapies for metastatic CRPC. Within the next 2 years, we should have answers to the questions regarding how best to sequence and combine these approved agents. Currently, there may exist concerns about whether combining these agents could lead to undue clinical and financial toxicities.

As noted in the proceedings of the St. Gallen Advanced Prostate Cancer Consensus Conference in 2015, we are still awaiting the results of large-scale prospective studies that can inform us how to optimally sequence the new agents we have to treat metastatic CRPC. Identifying predictive markers for selecting patients for these therapies is also an ongoing research area of interest will assuredly assist our goal of achieving precision medicine.[11] Discovering predictive markers for response to our current therapies is especially crucial since there exists increasing evidence that some castration-resistant phenotypes are more responsive to hormonal strategies, while others may be more effectively treated with cytotoxic chemotherapy.

Effective combination therapies may also improve outcomes of both progression and survival, while hopefully preventing toxicities and their attendant use of inpatient and emergency department services.[12]

1. Tannock IF, de Wit R, Berry WR, Horti J, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-1512.

2. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer for the IMPACT Study Investigators. N Engl J Med 2010;363:411-422.

3. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005.

4. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2): 152-60.

5. Steer HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012; 367(13): 1187-97.

6. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014; 371(5):424-33.

7. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. Lancet. 2010;376(9747): 1147-54.

8. Hoskins P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol. 2014; 15(12): 1397-406.

9. Crawford ED, Stone NN, Yu EY, et al. Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology. 2014;83(3):664-9.

10. Shore ND, Radium-223 dichloride for metastatic castration-resistant prostate cancer: the urologist's perspective. Urology. 2015 Apr;85(4):717-24.

11. Gillessen S, Olin A, Attard G, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol. 2015 Aug;26(8):1589-604.

12. Saad, F. Carles, J. Gillessen, S. et al. Radium-223 in an international early access program (EAP): Effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients. J Clin Oncol 33, 2015 (suppl; abstr 5034).

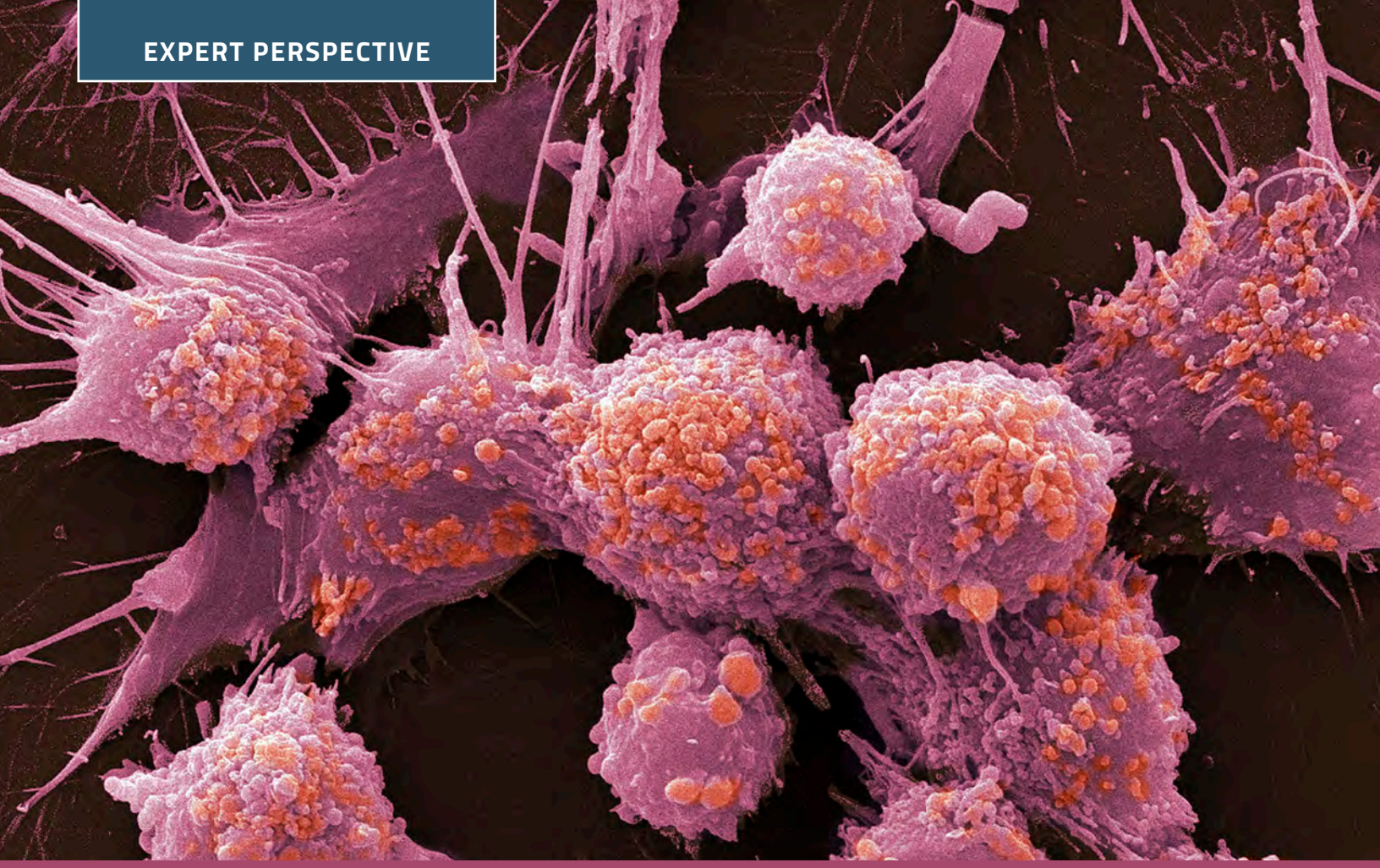
ONC TODAY®

YOUR ONCOLOGY NEWS & EDUCATION RESOURCE

Brought to you by the publishers of Everyday Urology and UroToday.com, a new site for medical oncologists that allows free, convenient access to daily aggregated content by tumor type.

SIGN UP TODAY TO RECEIVE NEWS AND UPDATES VIA EMAIL PERSONALIZED BASED ON YOUR PREFERENCES

OncToday.com



The Changing Role of the RADIOLOGIST/NUCLEAR MEDICINE PHYSICIAN in the Management of Advanced Prostate Cancer Patients

By Phillip Koo, MD

The several new therapies recently approved for the treatment of metastatic castrate resistant prostate cancer patients have altered the roles of various healthcare providers practicing in this space. For example, urologists have become more actively involved in the management of castrate resistant prostate cancer patients.

With regards to imaging, the advances in therapy have created an urgent need to develop better technologies to detect and monitor metastatic disease. Radiology and nuclear medicine practices are also changing as we expand beyond diagnostic imaging to include more longitudinal therapeutic care to our patients through the administration of radium 223 to our castrate resistant patients with symptomatic bone metastases.

DIAGNOSIS

One of the main goals for radiology and nuclear medicine in diagnosis is to provide the patients with the right test, at the right time. By serving as the stewards for imaging, we must strive to perform quality imaging by ensuring accuracy, timeliness, and patient safety throughout the entire process. We must also make every attempt to maximize the information obtained from imaging to lead to improved clinical outcomes.

The search for the right test is still underway, but there is much hope with new radiopharmaceuticals for prostate cancer such as F-ACBC (Axumin), which was recently approved by the FDA, and new PET based PSMA radiopharmaceuticals. The improved sensitivity and specificity of these exams at lower and lower PSA levels are very exciting, but this alone is not enough. It will be up to the imaging community, in close collaboration with our colleagues in urology and oncology, to design robust studies to demonstrate the clinical benefit and impact of imaging on outcomes. The utility of imaging will also extend beyond just disease detection to include the use of imaging as a prognostic tool and biomarker for treatment response/progression.

The radiologist/nuclear medicine physician also needs to become more involved in the development of more comprehensive and up to date appropriateness criteria for imaging prostate cancer patients in different stages of disease. Current guidelines and recommendations often focus solely on imaging at diagnosis and biochemical recurrence, but we know that the biology of disease in the castrate resistant setting is completely different. This gap was addressed by the RADAR Group recommendations in 2014, and it is clear we need better tools and better data through clinical trials to fully realize the potential of diagnostic imaging in advanced prostate cancer.

THERAPY

With regards to therapy, FDA approval of radium 223 significantly changes the treatment landscape for radiologists/nuclear medicine physicians for two reasons: 1. Unsealed sources of radiation therapy in prostate cancer are no longer just palliative, but they have been proven to improve overall survival. 2. Radium 223 is administered in a longitudinal fashion over 20 weeks rather than a single visit. This change in paradigm requires several changes to the traditional practice of radiology and nuclear medicine.

First, we need to create more patient friendly clinics. Most radiology/nuclear medicine practices were not designed to accommodate physician-patient interactions. Dedicated clinic space is required to allow for patient interviews and exams. Though radium 223 has a very good safety profile, radiology/nuclear medicine practices still need to develop the infrastructure to communicate with patients and manage adverse events. Radiology/nuclear medicine practices also need to actively manage the financial aspects of high cost therapies to help patients understand the costs involved, provide access to financial assistance, if possible, and manage the financial implications/risks for our respective practices.

Secondly, our practices need to become more ''provider friendly.'' Whether over the phone, through email, or the electronic medical record, radiologists/nuclear medicine physicians need to be available to provide consultative services with regards to the appropriateness of the therapies, risks/benefits, and radiation safety. Additionally, we should be active participants in tumor boards and multidisciplinary clinics to establish ourselves as valued contributors in the management of advanced prostate cancer patients. This will require more learning about many of the other therapies in prostate cancer which will allow us to dialogue with colleagues to identify the optimal patients for these life prolonging treatments. Radiologists/nuclear medicine physicians need to expand their consultative responsibilities beyond standard dictated reports.

Third, radiology/nuclear medicine must become more involved in therapeutic clinical trials. The inability to recruit patients into trials is often cited as the main factor why this is not possible. I believe this can be overcome through strong relationships and communication with the entire care team. Contributions to the design, implementation, and analysis of clinical trials will be important ways in which we can meaningfully contribute to the advancement of patient care.

In conclusion, it is a very exciting era in advanced prostate care for all healthcare providers involved. Whether we are dealing with imaging technologies or therapeutic agents, the radiologist/nuclear medicine physician must continue to engage all of the members of the care team and establish themselves as a vital and valued contributor. As roles change, I am constantly reminded that our ultimate goal is to create a better experience and a better outcome for our patients. With this guiding principle, I have no doubt that we can all continue to adapt and improve our practices accordingly. ■

"Opportunities multiply as they are seized."
– SUN TZU

Considerations in the USE OF ANDROGEN DEPRIVATION THERAPY for the Treatment of Men with Advanced Prostate Cancer

AN INTERVIEW WITH THOMAS KEANE

By Thomas Keane, M.B.B.Ch.

It was October 20, 2010, when the U.S. Food and Drug Administration asked manufacturers to add new warnings to labeling of gonadotropin-releasing hormone (GnRH) agonists, a class of drugs primarily used to treat men with prostate cancer. The warnings alert patients and their health care professionals to the potential risk of heart disease and diabetes in men treated with these medications. An analysis demonstrated that patients receiving GnRH agonists were at a small increased risk for diabetes, heart attack, stroke, and sudden death.[1]

The new labels included this update in the Warnings and Precautions section about these potential risks. Since this time urologists, medical oncologists and cardiologists have been assessing the effects of androgen deprivation therapy (ADT). The ongoing inquiry seeks to clarify if the type of medication and patient characteristics, such as age and comorbidities, impact cardiovascular disease (CVD) risk associated with ADT? And further how to assess the increased cardiovascular risk associated with current agonist or antagonists GnRH medications?

Studies over the past few years have been published which demonstrate that prostate cancer patients' comorbidities can impact. So it's important for urologists to consider these factors when treating men with advanced prostate cancer using ADT.

To gain an in-depth perspective on the CVD risks associated with ADT use, and how to best use these therapies in treating advanced prostate cancer, Everyday Urology™, interviewed expert Thomas Keane MD, professor and chairman of urology at the Medical University of South Carolina.

''We should not use a 'one size fits all' approach when using ADT. Different options should be made available and fully discussed with advance prostate cancer patients, and we should individualize our treatment choices,'' Dr. Keane said.

Dr. Keane noted that the first data on CVD risks associated with hormonal therapies in prostate cancer was published in 1967 by the Veteran's Administration.[2] Estrogens had proven to be effective for reducing prostate-cancer related deaths in patients with advanced hormone sensitive disease but using oestrogens also caused an increased incidence of deaths from cardiovascular disease. ''Not only were patients dying from myocardial infarction, but also pulmonary emboli,'' Dr. Keane said.

Use of ADT using LHRH agonists (or GnRH agonists) for prostate cancer has been a step forward for effectively treating advanced prostate cancer, but there are still significant cardiovascular morbidities and mortality associated with these medications. In 2015, for instance, a population-based study showed that among 9,596 patients from the Surveillance, Epidemiology and End Results (SEER) Medicare database, treated from 1991 to 2009 with ADT (LHRH agonists), the 5-year mortality from CVD was 9.8% and among those with pre-existing CVD, the mortality was even higher—14.8%.[3]

The CS21and CS21A phase III trials however, showed that the ADT alternative, the GnRH antagonist, degarelix—was at least as effective as GnRH agonists with less cardiovascular disease complications. The results from the CS21 trial showed that degarelix, when compared to the GnRH agonist leuprolide, offered faster testosterone suppression and PSA reduction and similar incidence of acute adverse events at 1 year. It also showed a lower rate of PSA failure in favor of degarelix but this was a secondary endpoint and the design of the trial was for non-inferiority On the basis of these results, the FDA approved degarelix in 2008. A later analysis of the CS21 trial data also showed that ischemic heart disease—the most frequent cardiac disorder in the trial—occurred in 4% of degarelix patients vs. 10% of leuprolide patients. Myocardial ischemia, myocardial infarction, and cardiac failure each occurred in less than 1% of those on degarelix vs. 2% of leuprolide patients.[4] CS21A data also revealed that degarelix offered improved disease control and superior PSA progression-free survival when compared with leuprolide.

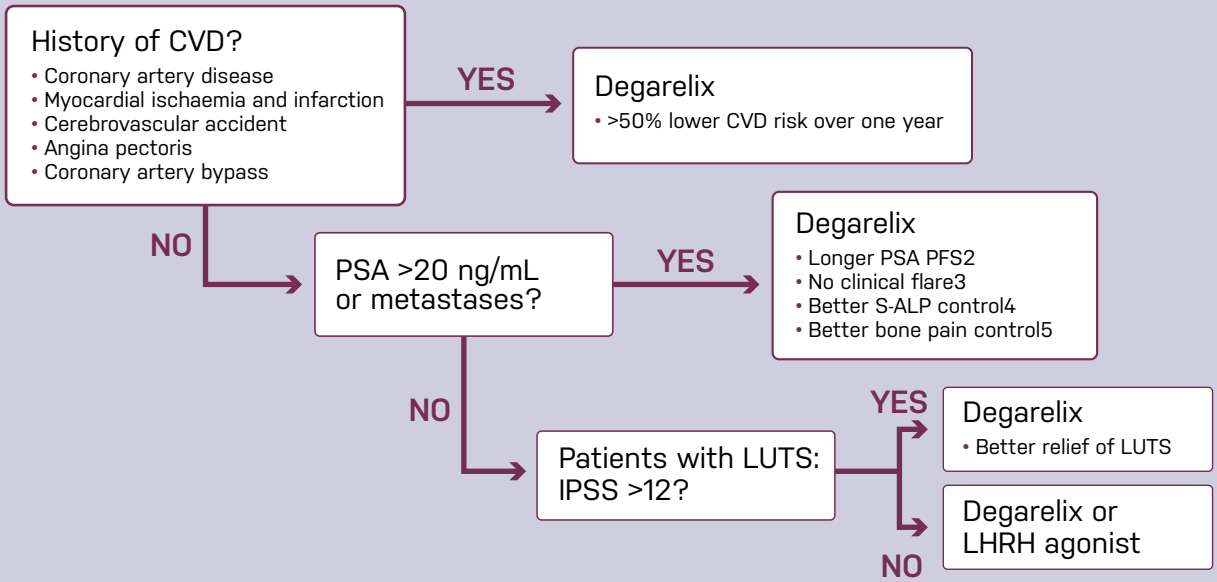
Dr. Keane points out that the incidence of both cardiovascular disease and prostate cancer is increased in older men (over age 60), and men with both prostate cancer and pre-existing cardiovascular disease have an increased risk of death—even when type of therapy was not assessed in recent studies. Yet when the use of GnRH agonists has been considered, the risk of cardiovascular morbidity and mortality for men with advanced prostate cancer on these medications or in those who received both GnRH agonists and radiotherapy, has been increased in both men over age 65 and in patients with moderate and severe comorbidities.[5,6]

Knowing which patients are most likely to suffer adverse cardiovascular effects from ADT therapy is one part of helping patients choose the best type of therapy for their advanced prostate cancer, Dr. Keane says. Results from a pooled analysis of six different randomized phase IIII and IIIB trials of degarelix or GnRH agonists has also offered specific guidance on the cardiovascular morbidities and mortality seen with these two types of ADT.

''This analysis was very significant, because it gave us a lot of data—not just on the morbidity associated with degarelix vs. GnRH agonists—but also on the relationship between ADT and pre-existing cardiovascular disease,'' Dr. Keane said. While a randomized trial would be best, in the absence of such, this data is the best we currently have.

In the study, published in European Urology, in 2014, cardiovascular risks, cardiovascular events and deaths from cardiovascular disease were assessed over 1 year following initiation of ADT therapy.[7] Men with certain risk factors for cardiac disease—such as a prolonged baseline QT, a corrected QT interval, hypokalemia, or a family history of long QT syndrome were excluded from the analysis. Cardiovascular events were defined

Androgen Deprivation Therapy Algorithm



as arterial embolic or thrombotic event, hemorrhagic or ischemic stroke, myocardial infarction and other ischemic heart disease.

Of 2328 patients, 1491 received degarelix and 837 received a GnRH agonist, either goserelin or leuprolide. Among the degarelix patients, 2.5% experienced a cardiovascular event, while 4.7% of these on GnRH agonists sustained a cardiac event. Among degarelix patients, 1.7% experienced a serious cardiac event—an event considered life threatening or one that required hospitalization. By contrast, 2.9% of patients on a GnRH agonists experienced a serious cardiac event. Patients in the degarelix group were also less likely to die over one year than those in the GnRH agonist group (HR=.47).

The difference in cardiovascular event or death was especially pronounced in men with baseline cardiovascular disease. Degarelix appeared to halve the number of cardiac events experienced by men with preexisting cardiovascular disease during the first year of ADT when compared to GnRH agonists. The effect of degarelix remained even when the results were adjusted for common cardiovascular disease variables and risks, such as statin medicine use, hypertension, high cholesterol, type 2 diabetes, age and BMI.

A Swedish study also shed light on the timing of cardiovascular disease after the administration of ADT.[8] In a study of 10,656 men on antiandrogens, 26,959 on GnRH agonists, and 3,747 who underwent surgical orchiectomy for prostate cancer, men with prostate cancer on GnRH agonists were at greater risk for a cardiovascular disease event than those who underwent orchiectomy 2 years after initiating ADT or surgery. Men who had experienced CVD events prior to surgery or ADT were at the greatest increased risk for cardiovascular events.

Yet time on ADT also had an impact on CVD risk in the study. Among men on ADT, CVD peaked sharply during the first year after initiation of therapy as well as for those who underwent surgical orchiectomy. "These observations imply that the majority of cardiovascular events occur shortly after the start of ADT, potentially because of an acute direct drug effect…" the researchers wrote in their study. The observation that cardiovascular events seem to peak right after the start of ADT has implications for clinical practice—and may affect the use of neoadjuvant and adjuvant ADT as well as palliative ADT, the researchers concluded.

As an increasing amount of research has provided details about the increased risk of CVD with ADT, studies have also delved into the possible mechanisms of this increased risk, according to Dr. Keane. Most acute CVD events are caused by rupture of a vulnerable atherosclerotic plaque. "The most vulnerable plaque is one with a thin cap and one that is rich in inflammatory cells and rich in lipids," Dr. Keane said. GnRH agonists and antagonists have different biological effects on T cells—which express GnRH receptors—these differences could lead to a difference in cardiovascular disease risk, he added.

GnRH agonists cause T cells to increase activity and proliferation, and one result is fibrotic cap disruption and plaque instability. By contrast, GnRH antagonists cause a complete blockade at the T-cell GnRH receptors with no signal transduction. As a result, stimulated responses are inhibited—potentially leading to less fibrotic cap disruption and plaque instability, according to Dr. Keane.

Since the increased CV risk from ADT therapy is so pronounced among men with pre-existing cardiovascular disease, recent laboratory and animal studies have also investigated the effects of different types of ADT therapy on established plaques. In one study in ApoE-/- mice, researchers looked at the effects of GnRH agonists and antagonists on advanced and stable plaques in the carotid artery.[9]

After 4 weeks of ADT, increased areas of necrosis were found

in stable plaques from leuprolide-treated mice when compared to degarelix-treated mice or controls (11% vs. .2% vs. .6%). ''Necrosis destabilizes plaques and increases the risk for rupture and development of acute cardiovascular events,'' the researchers wrote in their paper. Plaques from mice treated with leuprolide also showed evidence of increased inflammation as evaluated by macrophage immunohistochemistry, but there was no evidence of inflammation in plaques from degarelix-treated or control mice.

In addition to delving into the mechanisms that underlie the CVD risk seen with ADT therapy, recent studies have also pointed out that assessment for previous cardiovascular disease is vitally important in selecting patients for ADT therapy. A recent study in British Columbia, Canada, for instance, found that among 100 consecutive men with intermediate- or high-risk localized prostate cancer referred to the British Columbia Cancer Agency for ADT therapy, 25% had established cardiovascular disease.

Even among those without established cardiovascular disease, the risk for CV event was increased. This finding could be explained by the fact that Framingham risk scores that were high in 65% of patients in the study, intermediate in 33% of patients and low in just 1% of patients. Comorbidities that could affect CVD risk were also increased in the study population with hypertension present in 58% patients, dyslipidemia in 51% and impaired glucose tolerance or diabetes in 24%. Yet very few patients in the study had undergone any kind of testing for cardiac disease.

Only 35% had undergone ECGs, a relatively insensitive method for testing for silent cardiac disease. Also, just 6% of patients studied had further cardiac testing for cardiac ischemia with exercise treadmill tests or myocardial perfusion imaging.[10]

This kind of pre-existing cardiovascular disease points out the need for multidisciplinary care—including testing from cardiologists for patient who merit it—as well as improved patient selection for ADT therapies, according to Dr. Keane and recent research studies.

In one study presented at the 2015 ASCO Genitourinary Cancers Symposium, a large multiyear retrospective analysis of German health insurance data showed that men with prostate cancer treated with ADT—particularly GnRH agonists—had an increased occurrence of serious cardiovascular events as well as relevant baseline cardiovascular diseases.[11] In the study, the investigators identified 44,166 men with prostate cancer of whom 10,611 were treated with ADT. The majority, or 10,554 men, received a GnRH agonist, while the rest received a GnRH antagonist. Among those who received any kind of ADT, 7.8% experienced acute coronary syndrome or ischemic stroke vs. 5.9% of those who did not receive these medications. In the small group of patients receiving a GnRH antagonist, degarelix, the cardiovascular event rate was low at 2.3%—and all events occurred among men with a high-risk profile.

The investigators also identified an increased prevalence of baseline diabetes, coronary artery disease and heart failure among the ADT-treated patients vs. a non-prostate cancer reference group. Because of the frequent comorbid cardiovascular risk factors, another study by the same research group looked at coordination of care among treating specialists. Although they found that in German clinical settings, urologists are ''important partners in the detection and observation of cardiovascular morbidity,'' vigilance from cardiologists was far from ideal. The rate of concomitant cardiology treatment of ADT patients was just 28.8%, according to the study.[11]

While degarelix is not yet considered a standard of care for ADT treatment in advanced prostate cancer, it can be the best choice for men with pre-existing cardiovascular disease or risk factors for CVD. Likewise, patients with higher PSAs and more advanced disease will get the maximum benefit from degarelix due to this medication's superior effects on PSA progression, Dr. Keane said.

The GnRH agonists, however, offer improved convenience since they can be given at 3, 6 or 12 months, and the GnRH antagonists requires a monthly 28-day dosing regimen. ''For patients who want that convenience, or who are unable to visit a physician very often, the GnRH agonists can be a good choice—if they also have no history of CVD and small volume metastatic disease,'' Dr. Keane added. Finally, the appropriate way to resolve the remaining questions is conducting a prospective randomized controlled clinical trial and just such a trial is currently accruing. This is a Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease (PRONOUNCE).[12]

Meanwhile as we await results on this study, we have guidance from the other analysis to guide us in daily clinical practice decisions. ■

1. FDA: Include warnings on risk for class of prostate cancer drugs. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230334.htm last accessed 8/02/16.

2. Veterans Administration Co-operative Research Group. Treatment and survival of patients with cancer of the prostate. Surg Gynecol Obstet 1967; 124: 1011-7.

3. Gandaglia G, Sun M, Popa I, et al. Cardiovascular mortality in patient with metastatic prostate cancer exposed to androgen deprivation therapy: A population-based study. Clin Genitourin Cancer. 2015; 13 (3): 123-30.

4. Shore ND. Experience with degarelix in the treatment of prostate cancer. Ther Adv Urol. 2013; 5 (1): 11-24.

5. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol. 2007; 25 (17): 2420-5.

6. D'Amico AV, Chen MR, Renshaw AA, et al. Androgen suppression and radiation vs. radiation alone for prostate cancer: A randomized trial. JAMA. 2008; 299 (3): 289-95.

7. Albertsen PC, Klotz L, Tombal B, et al. Cardiovascular morbidity associated with gonatropin releasing hormone agonists and an antagonist. Eur Urol. 2014; 65: 565-73.

8. O'Farrell S, Garmo H, Holmberg L, et al. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol. 2015; 33: 1243-1251.

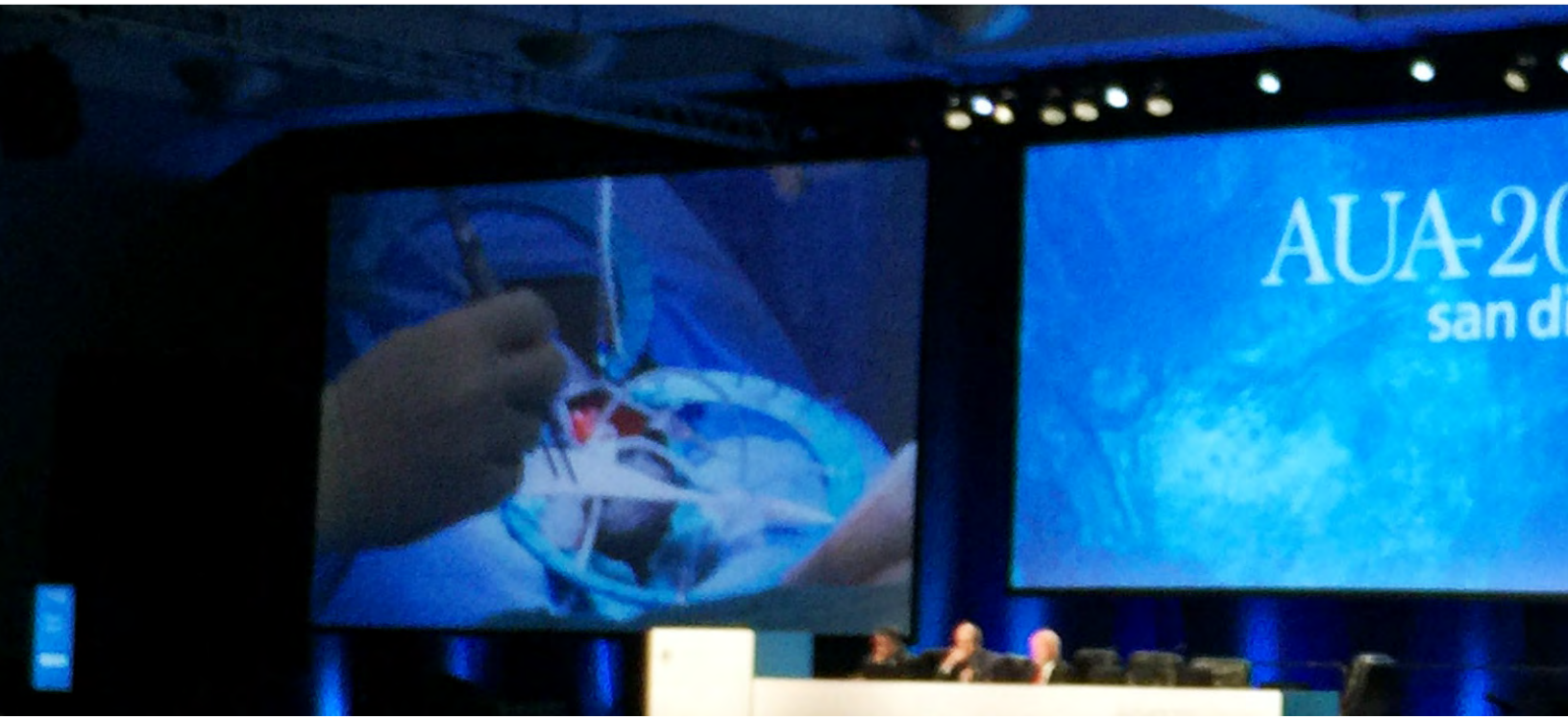
9. Knutsson A, Hsiung S, Celik S, et al. Treatment with a GnRH receptor agonist, but not the GnRH receptor antagonist degarelix, induces atherosclerotic plaque instability in ApoE-/- mice. Nature Scientific Reports. 2016 May 18; 6: 26220.

10. Davis MK, Rajala JL, Tyldesley S, et al. The prevalence of cardiac risk factors in men with localized prostate cancer undergoing androgen deprivation therapy in British Columbia, Canada. Journal of Oncology. 2015; 2015 Article ID 820403.

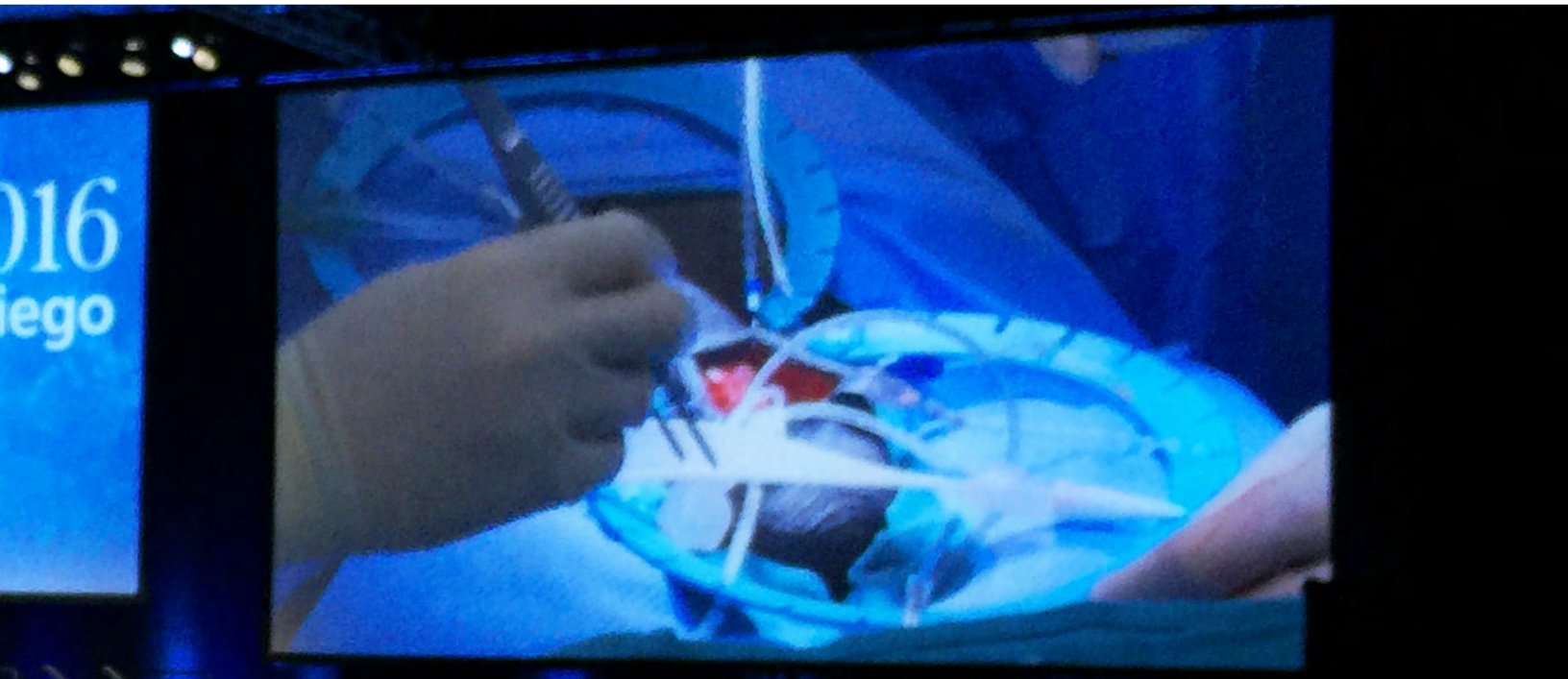
11. Russel C. Androgen deprivation therapy and cardiovascular risk. At: http://meetinglibrary.asco.org/content/106160?format=format=posterlmg

12. A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease (PRONOUNCE) https://clinicaltrials.gov/ct2/show/NCT02663908?term=pronounce&rank=1 Last accessed 08.02.2016


AUA
2016
san diego
Urology Care
OUR FOUN TION,
Because Care.
American
Urological
Association


AUA-20
san di


Registration
AUA-2016
san diego
SHARING KNOWLEDGE. SETTING STANDARDS.
Badge Holder Pick Up
Housing
Grand Reception
Course Passes
AUA-2016
san diego
Men

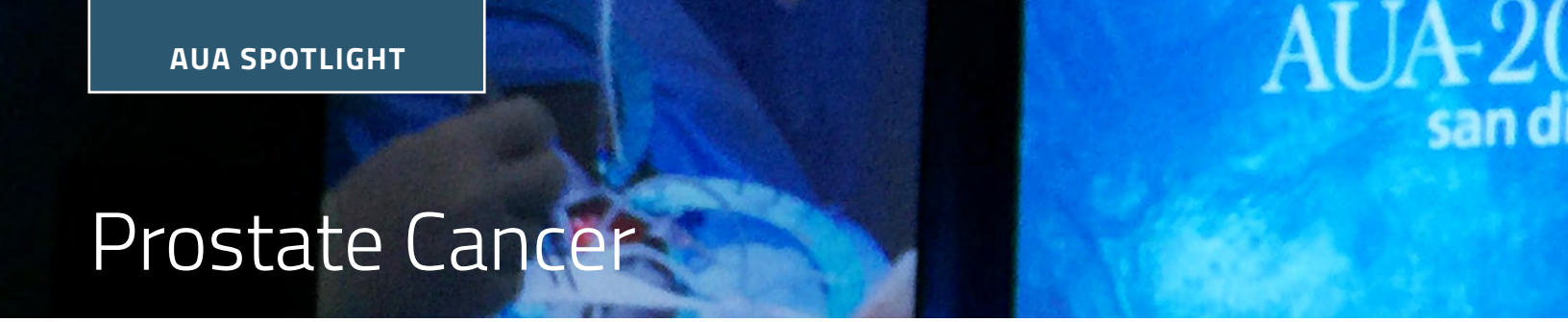


AUA 2016 // MAY 6-10, 2016 // SAN DIEGO, CA

Conference highlights provided by urologic oncology fellows and students from the Fox Chase Cancer Center and the University of California, Irvine.

The coverage is segmented into five of the tumor types covered: prostate cancer, bladder cancer, kidney cancer, penile and testicular cancer. Content also includes new findings on a new imaging agent that allows for diagnosis of recurrent prostate cancer, immunotherapy in bladder cancer, developments in surgical procedures and a variety of other advancements.

We welcome you to read additional conference coverage from the AUA 2016, or other conferences at www.urotoday.com/conference-proceedings



Prostate Cancer

Primary Screening—Time to Change?

Dr. Stacy Loeb, MD presented on the controversy of prostate cancer screening. Mathematical models suggest about 45-70% reduction in prostate cancer mortality due to PSA-era screening. However, we have conflicting results from randomized-controlled trials. PLCO trial suggested no difference in prostate cancer mortality between organized screenings versus usual care. However, the data from this trial is limited due to a high level of controls who have had at least 1 PSA screening before or during the trial. ERSPC trials suggest 21% reduction in prostate cancer mortality at 13 years.

The conflicting results from trials lead to most extreme recommendations by 2012 USPSTF, which recommended against any PSA screening for men of all ages. This was subsequently echoed in 2014 by Canadian Task Force. However, neither of these task-force included prostate cancer specialists.

Modeling studies suggest that the consequences of these task force recommendations may eliminate overdiagnosis at the expense of 2-fold increase rate of metastatic cases and 13-20% increase in prostate cancer deaths by 2025.

Surveys on patient reactions to USPSTF guidelines suggest that only 13% planned to follow the USPSTF recommendations. Additionally, several medico-legal cases of prostate cancer identify failure to perform an initial PSA test and failure to follow-up of an elevated PSA as the two leading reasons for a lawsuit.

Shared Decision-Making may be the paradigm. AUA, EAU and NCCN recommend this approach. Shared decision-making involves discussion of the risks of benefits of PSA screening as well as discussion of patient preferences. Studies suggest that this is under-utilized with only about 8% of patients polled in National Health Interview Survey reporting that a shared-decision making took place. What is concerning is that 88% of unscreened men reported no discussion on PSA screening.

Optimal screening paradigm involves discussion of baseline PSA, individualized screening intervals, utilization of markers of greater specificity, and using a multivariable, risk-adapted approach.

Baseline PSA in young men is important. PSA>0.7 in men in their 40's is a strong predictor of prostate cancer risk than family history, race or DRE (Loeb et al, Urology 2006).

Screening frequency is variable different in AUA, EAU and NCCN recommendations and needs to be personalized to a patient.

PSA isoforms can be used to better predict prostate cancer risk. Higher rate of free PSA illustrate lower risk of prostate cancer. Prostate Health Index (PHI) can be used to predict probability of finding cancer, poor prostatectomy outcomes and progression during surveillance. 4K score (consisting of total PSA, free PSA, intact PSA, and hK2) has shown improved specificity for finding clinically significant prostate cancer on biopsy. Urinary markers can also be used. PCA3 has been approved by FDA but only for recommendation for a repeat biopsy. These urinary markers need head-to-head comparative studies.

Numerious nomograms can combine several clinical variables to assist in clinical decisions. These combine life expectancy, comorbidities, prostate volume, family history, race and prior biopsy history.

In conclusion, improving care of prostate cancer involves better patient selection (selecting those with long life expectancy), better screening (baseline PSA in 40's, using more specific markers, using risk-adapted nomograms), better biopsy (reducing infection risk and increasing the yield of a positive biopsy using imaging such as mpMRI), and better treatment (more active surveillance for low-risk and reducing treatment-related morbidity). A balanced approach is needed . In Pre-PSA era, we had increased metastatic disease incidence and increased prostate cancer deaths. In PSA-era we have increased inappropriate testing and wide-spread overtreatment. In future, we need more balanced screening with selective, personalized risk-adapted strategies.

PRESENTED BY: STACY LOEB, MD, AT THE 2016 AUA ANNUAL MEETING - MAY 6 - 10, 2016 – SAN DIEGO, CALIFORNIA

WRITTEN BY: MOHAMMED HASEEBUDDIN, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

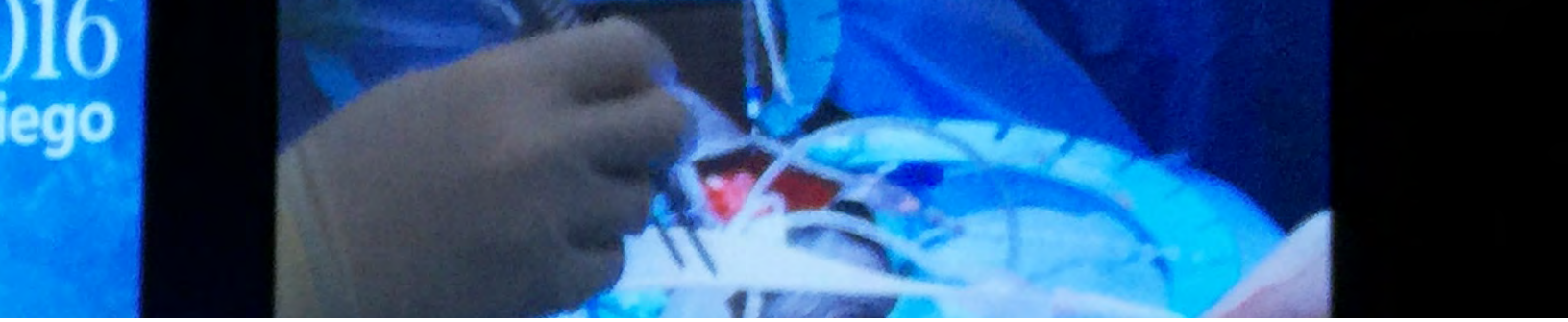
Eye of the Beholder: Is Delayed Treatment on Active Surveillance a Success or Failure?

Dr. Laurence Klotz from Toronto critically analyzed the outcomes of the Active Surveillance for low to intermediate risk prostate cancer.

Currently, there is a greater recognition of an overtreatment problem and effect on quality of life with treatment. We also know the nature of occult high grade disease. New biomarkers and multiparametric MRI are also having an impact on Active Surveillance and may allow us to identify those who can be placed on surveillance or treated.

Active Surveillance is a success when it avoids mortality and disease related morbidity while at the same time avoiding QOL side-effects.

We are beginning to realize that the metastatic potential of Gleason Score 3 is about zero. Molecular genetics of GS 3 resembles normal cells with a molecular signature distinct from aggressive cancer cells. The major limitation of current active surveillance strategies relate to pathologic miss of coexistent higher grade cancer. Dr. Klotz then poses the question: "If GS 3 does not metastasize, why does volume of GS 3 matter?" He answers that the high volume is a marker for the presence of higher-grade cancer. Under-staging is a major limitation and hopefully mpMRI may allow us to identify clinically significant cancer.



Current predictors of disease reclassification during active surveillance are increased PSA density, race and % core involvement. In their Toronto series, the 15 year CSS is about 5%. Their protocol for AS currently allows for low volume intermediate prostate cancer. However, recent analysis of data suggest a lower Overall Survival, Cancer Specific Survival, and metastatic free survival with any GS 4 component.

The Hopkins protocol is more restrictive and only allows for Epstein criteria (no Gleason pattern 4). Therefore, the 15 year CSS is low at 0.5%.

About 20% of patients who presents with prostate cancer would qualify for Hopkins protocol versus about 50% in the Toronto protocol. Current paradigm of identification for AS is pathological from biopsy and risk stratification. Imaging may change this and may allow us to more accurately identify those who may benefit from AS.

Dr. Klotz concludes that clear candidates for AS include patients with GS6 with non-extensive disease, non-suspicious MRI, and low PSA density. The grey areas are patients with extensive GS6, GS 6 in men < 50 years and GS 7 with < 10% tumor involvement.

In conclusion, the current protocol that Dr. Klotz adopts is:

- Eligibility: most GS 6, PSA< 15, selected GS 3+4 with low volume (<10%)
- Exceptions: High volume GS 6 in young patients, high psa density.
- Workup: MRI and targeted biopsy is done for all high volume GS 6, high PSA density, and any pattern 4 diseases.
- Follow-up: PSA q 6 months
- Confirmatory biopsy or MRI within 1 year. If MRI negative and low risk, biopsy is optional.
- Repeat MRI/biopsy q 3-5 years until age 80.

PRESENTED BY: LAURENCE H. KLOTZ, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MOHAMMED HASEEBUDDIN, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

USPSTF—Early Impact on Screening and Staging

Matt Cooperberg discussed the impact of the USPSTF Grade D recommendation on screening and staging. Along with rising incidence, there has been a 50% drop in age adjusted prostate cancer mortality since the early 1990s. Worldwide, there were 258,000 deaths in 2008, and this number has increased to 300,000 deaths this year.

Meanwhile, the expected rate of US incidence is down to 180,000 this year. While this still makes prostate cancer the most common cancer among men, this represents a decline in incidence and is likely attributable to the USPSTF Grade D Recommendation.

We know, based on data from ERSPC that there is a 21-29% relative reduction in prostate cancer morality (42% in Goteborg). We also know that PLCO is non-informative with respect to the question of screening vs no-screening as there was approximately 90% contamination in the control arm of PLCO, and that men in the control arm actually had more PSA tests than those in the intervention arm. This data should be disregarded from meta-analyses and policy recommendations. The grade D recommendation misrepresents the evidence on screening as it includes too short of a time-horizon; with a longer time horizon, the ratio of overdiagnoses: lives saved decreases 7-fold. However, in the purview of public health, the issue of over-diagnosis and over-treatment remains of ultimate importance and may have driven the decision; it's ultimately largely our fault.

Meanwhile we have made recent strides in improving our risk stratification for determination of who should receive treatment. Review of UCSF data shows a utilization rate of AS of 40% for low risk men, up from a historic rate of 10%. Early data from AQUA shows similarly encouraging results.

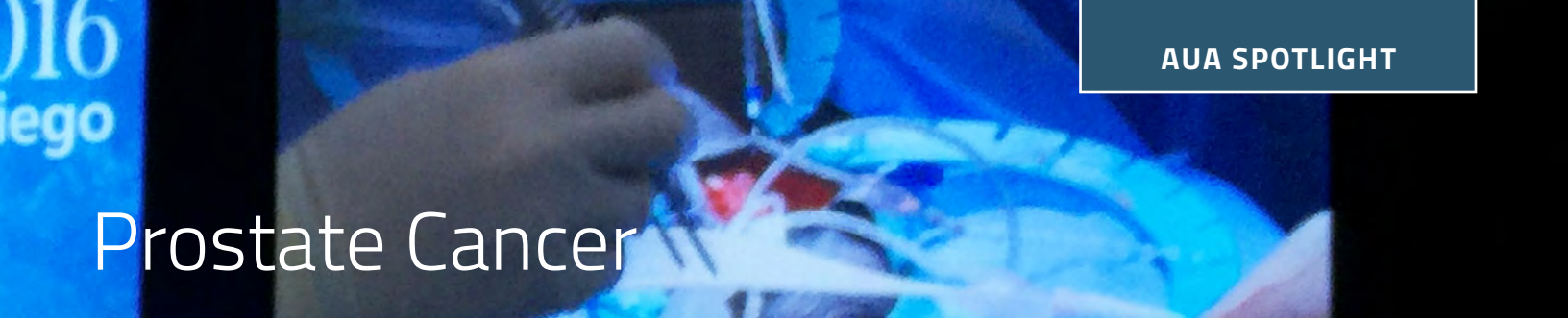
Study of PCP behavior with respect to PSA screening demonstrates no change between 2000 and 2005, as men in their 50s were under-screened and men in their 70s were over-screened. Similar trends are seen when comparing screening rates for 2005 and 2010. However, it appears that the vast majority (69%) of PCPs consider the USPSTF over ACS, AUA, and ACS guidelines. Barocas and colleagues demonstrated that the diagnosis count has decreased on a monthly basis and continues to decline since the release of the grade D recommendation.

While we are over-diagnosing fewer low risk men, we are also under-diagnosing high risk disease. If we were to stop screening altogether, we would be back to where we were in the 1980s in terms of patients presenting with locally advanced and metastatic disease.

In conclusion, the USPSTF analysis downplayed benefits, overstated harms, and was predicated on too short of a time horizon. Overtreatment is certainly an issue, but this may have been traded for under-treatment, which represents a potentially more dangerous public health crisis. The answers lie in smarter screening and better treatment decisions. Finally, Dr. Cooperberg encouraged ownership of the data to promote ownership of the truth.

PRESENTED BY: MATT COOPERBERG, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: DR. NIKHIL WAINGANKAR, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA



Prostate Cancer

Long-term follow-up circulating tumor cells as predictors for survival in men treated with abiraterone acetate for castration resistant prostate cancer following chemotherapy

Advanced (including Drug Therapy) III session at the AUA 2016, described long term follow-up of circulating tumor cells (CTC) predictors for survival in men treated with abiraterone for mCRPC following chemotherapy.

Dr Christian Meyer reviewed that Circulating tumor cells (CTC) are established biomarkers able to predict response to chemotherapy (CTX) in metastatic castration resistant prostate cancer (mCRPC). In the COU-AA-301 trial cohort, a biomarker panel that include CTC was shown to be predictive of survival in men treated with abiraterone acetate after chemotherapy.

The authors enrolled 37 patients with mCRPC who progressed after at least one but not more than two prior chemotherapy regimens. Treatment included AA 1000mg daily plus prednisone 5mg BID and was continued until disease progression was identified or unacceptable toxicity. A full blood Cell save tube was drawn when patients were included in the study. Evaluation of CTC was performed according to the Cell Search Epithelial Cell Test protocol (Veridex, Raritan, NJ). Subsequent CTC measurements were done monthly on each follow-up visit.

Kaplan-Meier (KM) estimates and Cox regression analysis assessed the influence of independent predictors on overall survival. Mean patient age was 71.3 years, median PSA was 297 ng/ml and 20% and 8% of the patients had significant pain and visceral metastasis respectively. After a median (IQR) follow-up of 17.7 (9.4 – 31.9) months, 35 of 37 patients died. PSA declined by 30% and 50% in 45% and 37% of the patients.

A significant survival benefit was shown for patients with CTC counts <5 vs. >5 ($p<0.001$). Baseline PSA, hemoglobin, time under AA, number of systemic therapies after AA, discontinuation and CTC converters were significant predictors of OS on the univariable analysis. However, only time of treatment under AA and number of subsequent treatment lines (e.g. Enzaltuamid, Radium-223, Cabazitaxel) after AA were identified as independent predictors of overall survival on multivariable analysis.

The authors conclude that CTC >5 is an early indicator of disease progression. CTC counts failed to have significant association with OS in a multivariate context. Access to subsequent therapies provides proven survival benefit for men with mCRPC after chemotherapy and AA.

PRESENTED BY: CHRISTIAN MEYER, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MIKI HAIFLER, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

The Problem of Undertreatment of Men with High-risk Prostate Cancer

In this session, Dr. Cooperberg opened by noting a >50% drop in age-adjusted prostate cancer mortality since the early 1990s. This victory is attributable to early detection and better treatment. However, prostate cancer is a global killer and is rising.
So, what treatment is best?

Based on PIVOT trial, one can argue that RP is more effective than watchful waiting alone. With regard to the question of radiation therapy versus surgery in high-risk men, the preponderance of data would suggest an approximately 50% risk reduction with surgery upfront compared to primary radiotherapy. This is most pronounced in intermediate and high risk disease with the best outcomes seen in multimodal therapy (surgery followed by radiation). Several randomized, controlled trials (RCTs) in this space are expected to return results in the next few years. For patients with M0 disease, some have considered neoadjuvant chemotherapy. CALGB 90203 is an RCT exploring this questions with results expected in about a year.

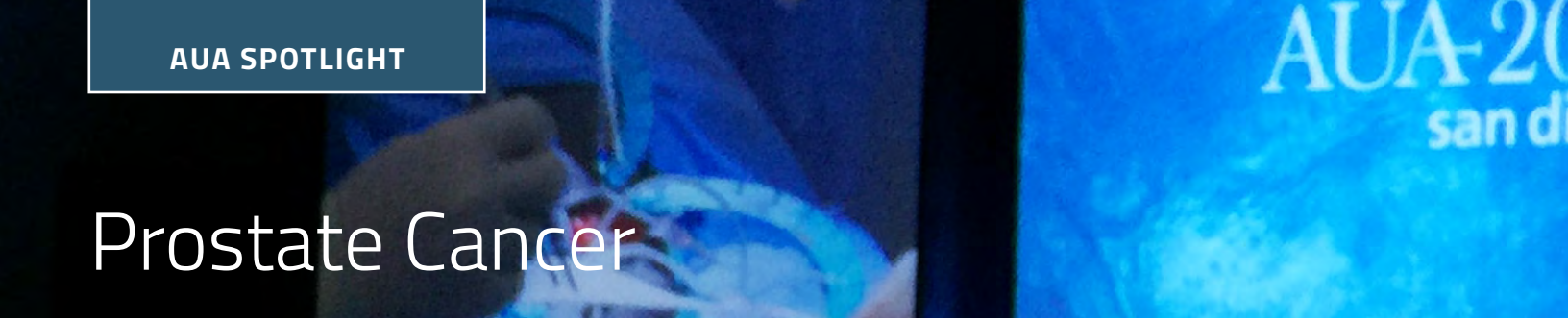
Perhaps the most important concept is the need to personalize decisions. Currently, we are at about 80% accuracy with risk stratification (CAPRA, D'Amico, etc) alone. However, perhaps the most relevant are the affymetric gene readouts offered by tests like decipher which is now available in both the biopsy and post-prostatectomy space.

Regardless, these questions must be answered. In the wake of the 2012 USPSTF grade D recommendation against the use of PSA screening, prostate cancer diagnosis across all risk types has occurred. On the one hand, this is a good thing since low risk disease is being diagnosed less frequently. However, a reduction in diagnosis of high risk disease will result in more metastatic disease (it is a mathematical certainty!).

In conclusion, Dr. Cooperberg summarized his talk by stating that there is a growing body of evidence suggesting a greater role for local therapy (including surgery) in high-risk prostate cancer. Aggressive multi-modal treatments need to be personalized and tailored to maximize both length and quality of life. High risk prostate cancer is increasingly treated aggressively in the US but many cases are still undertreated with ADT monotherapy. Delayed diagnosis is the worst undertreatment and our collective data must drive change at the policy level.

PRESENTED BY: MATTHEW R. COOPERBERG, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA



Prostate Cancer

The Impact of Infectious Complications after Prostate Biopsy on Radical Prostatectomy Surgical Outcomes: A Population-Based Analysis

Transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is the standard of care for prostate cancer diagnosis. However, infectious complications post-TRUS-Bx has increased in recent years. In effort to discern the affect of these complications on RP outcomes, Dr. Daniel Olvera-Posada conducted a population-based cohort analysis comparing surgical outcomes of patients who did or did not suffer from TRUS-Bx complications.

From April 2002 to March 2013, 27,637 patients undergoing RP in Ontario were identified, 711 of which experienced hospitalization due to urinary tract infection (UTI) or sepsis within 30-days post TRUS-Bx complications. The composite primary outcome was identified as surgical complication, post-operative treatment of urinary fistula, intestinal diversion, upper urinary tract obstruction or ureteral injury; the secondary outcome consisted of oncological, functional and hospital related events.

From these guidelines, patients with an infectious post-TRUS-Bx experienced a higher rate of composite primary outcome (OR 1.89, 95% CI 1.10-3.25, p=0.019), 30 day hospital readmission (OR 1.88, 95% CI 1.37-2.58, p<0.001), and blood transfusion (OR 1.74, 95% CI 1.44-2.09, p<0.0001), contributing to a lengthened hospital stay (p<0.0001). No differences, however, were found in the proportion of patients requiring adjuvant radiation, hormonal treatment, invasive therapies for incontinence or ED, or 30-day mortality rate.

Overall, this population-based study demonstrated that TRUS-Bx related infectious event is significantly associated with a higher risk of surgical complications, blood transfusion, readmission rate and prolonged hospital stays. While functional outcomes and need for other therapy appear similar post-RP, infectious complications post-TRUS-Bx may still negatively impact surgical outcomes.

With regards to clinical practice, researchers of this study suggested an increase in wait time post-TRUS-Bx infectious complications. Since oncological outcomes are not affected, an increase of wait time to 6 to 9 months may compel the surgeon to wait longer.

PRESENTED BY: DANIEL OLVERA-POSADA AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: LINDA HUYNH; BIOMEDICAL RESEARCH STUDENT, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Study of PSMA-Targeted 18F-DCFPyL PET/CT in the Evaluation of Men with an Elevated PSA Following Radical Prostatectomy

A very interesting poster was presented in Prostate cancer: advanced session at the AUA 2016 evaluating PSMA-Targeted 18F-DCFPyL PET/CT in the Men with an Elevated PSA Following Radical Prostatectomy. Dr Michael A. Gorin reminded all that PET/CT) utilizing radiotracers targeting prostate-specific membrane antigen is a promising novel method for imaging low volume sites of prostate cancer.

The authors sought to evaluate the utility of PSMA-targeted18F-DCFPyL PET/CT in men with an elevated PSA following radical prostatectomy. The study enrolled prostate cancer patient who had radical prostatectomy and serum PSA levels of 0.2-1ng/ml. these patients were imaged with CT or MRI of the abdomen, bone scan and 18F-DCFPyL PET/CT. Sensitivity analysis was performed on and on the 18F-DCFPyL PET/CT compared with the conventional imaging modalities. 20 men were included in the study and were imaged as previously described. Only 4 patients were diagnosed with more than 1 site of disease with the conventional imaging modality. On the other hand, 13 patients were found to have more than 1 foci of abnormal radiotracer uptake on 18F-DCFPyL PET/CT. of these 13 patients, 7 had a local recurrence, 14 had lymph node metastases and 1 had bony disease. 18F-DCFPyL PET/CT identified all disease site that were detected by the conventional imaging modalities. The authors conclude that 18F-DCFPyL PET/CT is a sensitive test to diagnose disease sites in man after radical prostatectomy and biochemical failure.

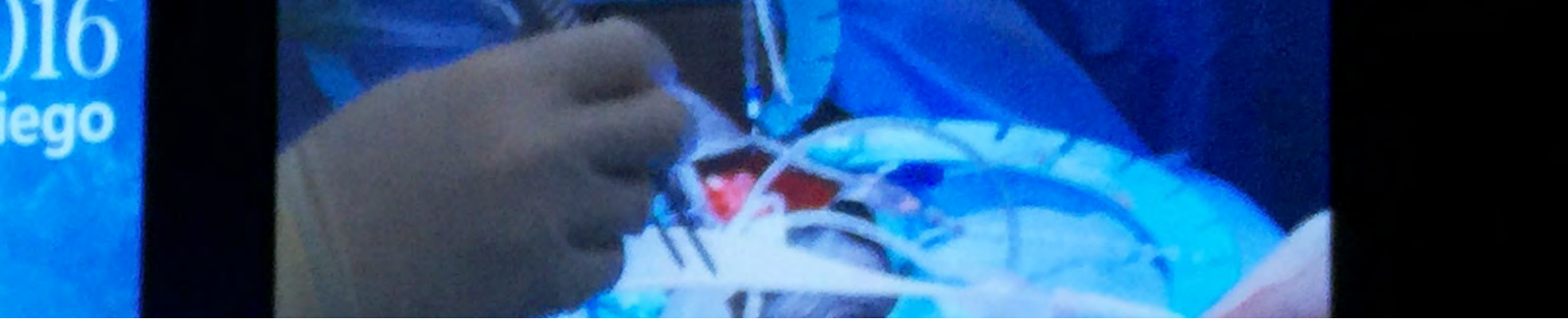
PRESENTED BY: MICHAEL A. GORIN, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MIKI HAIFLER MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Radium-223 re-treatment: Experience from an international, multicenter, prospective study in patients with castration-resistant prostate cancer and bone metastases

Dr. Luke Nordquist presented data evaluating the value of Radium-223 re-treatment in castration-resistant prostate cancer and bone metastases.

Radium-223 (Ra-223) treatment is beneficial in patients with castration-resistant prostate cancer (CRPC) with bone metastases. The authors sought to report the safety and efficacy of Radium-223 re-treatment from an international prospective open-label trial in metastatic CRPC patients (NCT01934790).



The study enrolled CRPC patients with more than 2 bony metastases who previously received Radium 223 treatment and progressed after inital treatment. No additional chemotherapies were given, but other agents were permitted (e.g. abiraterone).

The primary outcome of this study was safety, and time to radiographic bone progression, time to PSA progression, and radiographic progression-free survival (rPFS) based on MRI/CT and bone scans performed q 3 mo were included.

44 patients were included in the study and 66% of these patients received all 6 treatments.

73% of the patients failed either abiraterone or enzalutamide.

7% of the patients experienced grade 3 or 4 adverse events. Only 1 patient was reported to have radiographic progression.

Time to biochemical progression was 2 month and median rPFS was nearly 10 months. The authors concluded that Radium 223 re-treatment is safe and well tolerated. Re-treatment with radium-233 it provided continued stability in the bony disease.

PRESENTED BY: LUKE NORDQUIST, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MIKI HAIFLER MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Racial Variation in Patient-Reported Outcomes Following Treatment for Localized Prostate Cancer: Results from the CEASAR Study

With prostate cancer being the most common malignancy affecting men and various treatment options available such as surgery, radiotherapy, and even active surveillance, it is important to evaluate the functional outcome effects of therapies in the context of a diverse U.S. population. In this study from Vanderbilt University, the authors sought to evaluate outcomes following treatment for prostate cancer amongst African American (AA), Hispanic (H) and White (W) populations.

In this prospective cohort study, 3,708 men across the U.S. using SEER registries were followed after Radical prostatectomy, External Beam Radioatherapy and Active Surveillance treatments for localized prostate cancer using the self-reported EPIC-26 questionnaire at baseline, 6 months and 12 months. In the end, data was gathered from 2,338 men: 78.5% White, 13.9% African American, and 7.3% Hispanic.

The authors found that post-treatment urinary outcomes of irritability and incontinence, bowel irritability and sexual function did not vary dramatically based by race. Also, there were no statistically significant differences in bother with respect to urinary, bowel and sexual function based on race/ethnicity. Next, different demographic and social factors such as T-stage, PSA, education, marital status, etc. were evaluated in a model to test the predictive function of urinary incontinence at one year. As expected, race failed to show any predictive function, however, primary treatment selection and baseline function were shown to be the most predictive of urinary function.

The underlying hypothesis for the study stemmed from the 2004 PCOS report that African American men had improved recovery of urinary and sexual function compared to Whites after prostatectomy or radiotherapy. The author provides that in this prospective study of a large population-based cohort encompassed a larger patient sample, inclusion of an active surveillance arm and a more updated robotic experience that could explain the lack of racial differences in outcomes in this study.

PRESENTED BY: MARK TYSON, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BLANCA MORALES; DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

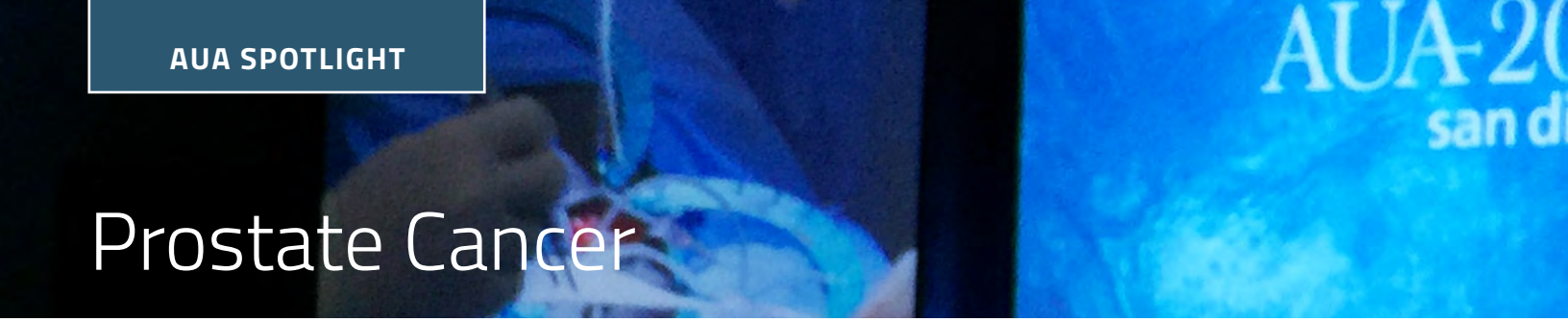
Repeat Biopsy: State-of-the-Art Patient Selection and Technique

In today's International Prostate Forum at the 2016 AUA, Dr. David Crawford discussed patient selection and technique for patients who undergo repeat biopsy. He began by discussing challenges in CaP detection, which include improvement of the interpretation of PSA, decreasing the rate of unnecessary biopsies, and enhancement in the risk stratification of newly-diagnosed patients.

Dr. Crawford illustrated 4 "buckets" to aid in these challenges: identifying who to biopsy (aided by PSA, PHI, 4K, SelectMDx), who to re-biopsy (aided by ConfirmMDx, PCA3, 4K), who to offer interventional therapy vs AS (aided by Decipher, OncotypeDx, Prolaris, ProMark), and who to treat or not treat post-prostatectomy (aided by Decipher and Prolaris).

Striking statistics underscore the need for enhancing patient selection for biopsy: 25% will receive a false-negative result, 15% will suffer complications, and 3% of patients will be hospitalized. Moreover, 43% of patients have a repeat biopsy, of which 44% have a second repeat biopsy, of which 43% have an additional biopsy. Meanwhile, more than ½ of cancers found on repeat biopsy are clinically significant.

An algorithm that may improve our ability to detect cancer and risk stratify patients begins with PCP-driven PSA screening and stratification by PSA > vs. < 1.5. Those with higher PSA are referred to a urologist where the test is repeated along with DRE. Those patients with abnormal exam or PSA undergo biopsy, and if negative, they



Prostate Cancer

(continued from page 31)

undergo testing with ConfirmMDx, PCA3, 4K, or PHI to aid in the decision to either re-biopsy or defer further investigation. Those with positive biopsies undergo OncotypeDx, ProMark, PTEN/ERG, or Prolaris testing, and KnowError to faciliate stratification by indolent vs aggressive disease. At this point, the decision for active surveillence vs intervention can be determined.

PHI test was shown to improve detection of high grade CaP (AUC 0.707) on rebiopsy compared to PSA alone (AUC=0.551). PCA3 is an FDA-approved urine based test with a score determined by PCA3/PSA mRNA; increasing PCA3 score is correlated with increasing risk of positive biopsy. 4K includes total, free, and intact PSA in addition to hK2. Age, DRE and prior biopsy status are taken into consideration, and the test result provides % risk of having aggressive prostate cancer for an individual patient. ConfirmMDx detects an epigenetic field effect associated with cancer at the DNA level, which provides actionable information to improve patient risk stratification and decisions on repeat biopsy; it facilitates ruling out cancer-free men from undergoing unnecessary repeat biopsy, and rules in those who require repeat biopsies and potential treatment. Pooled analysis of the MATLOC and DOCUMENT trials validate ConfirmMDx and demonstrate a 96% NPV for clinically significant cancers and 90% NPV for all cancers.

Dr. Crawford concluded that we need close collaboration between primary care physicians and urologists to optimize diagnosis, risk stratification, and management of prostate cancer patients. He presented an additional management schema to support this: PCP checks PSA, and if < 1.5, the patient gets it rechecked in 5 years. If > 1.5, the PCP should consider referral to a urologist. At this point, PHI, SelectMD, PCA3, or 4K score should be checked. If considered high risk the patient should undergo TRUS biopsy, followed by ConfirmMDx and possible MP MRI. If low risk, he should continue with routine PSA checks. Patients who are biopsied and are intermediate risk on biopsy should have genomic markers checked to stratify patients for treatment vs AS..

PRESENTED BY: DAVID CRAWFORD, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: DR. NIKHIL WAINGANKAR, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

What's Next for Radiation Therapy in Low to Favorable/Intermediate Risk?

Mack Roach, III MD, FACR gave a broad over-view of development within radiation oncology with a focus on low to intermediate risk prostate cancer.

He discussed RTOG9910 trial which illustrated no change in overall-survival, disease-specific survival or biochemical failure when intermediate risk patients were randomized to 4 months or 9 months duration of neoadjuvant ADT with XRT. He concluded that there is currently no reason to use ADT beyond 4 months in any patients with intermediate risk prostate cancer. Low-risk patients should get no ADT.

He then discussed RTOG0126 trial comparing 79.2Gy vs 70.2 Gy in intermediate risk prostate cancer patients. The study did not show any difference in overall or cancer-specific survival but improved biochemical control rate with higher dose.

Dr. Roach III then discussed an increased interest in SBRT as compared to IMRT. SBRT utilization is predicted to increase over next decade. SBRT is associated with more toxicity currently than IMRT but is shown to be less expensive with equivocal cancer outcomes. Therefore, further work is being done to minimize toxicity.

He then discussed proton-beam therapy, which is also projected to increase in utility. Although the cost is high with proton beam therapy currently, further work needs to be done to decrease the number of fractionations, which may make it financially feasible.

Dr. Roach III concludes with the following points:

- No ADT in the vast majority of low risk disease
- No more than 4 months in intermediate risk disesase
- SBRT is likely to grow
- Proton therapy is likely to grow if hypofractionation is achieved.
- MRI maybe helpful in patient selection

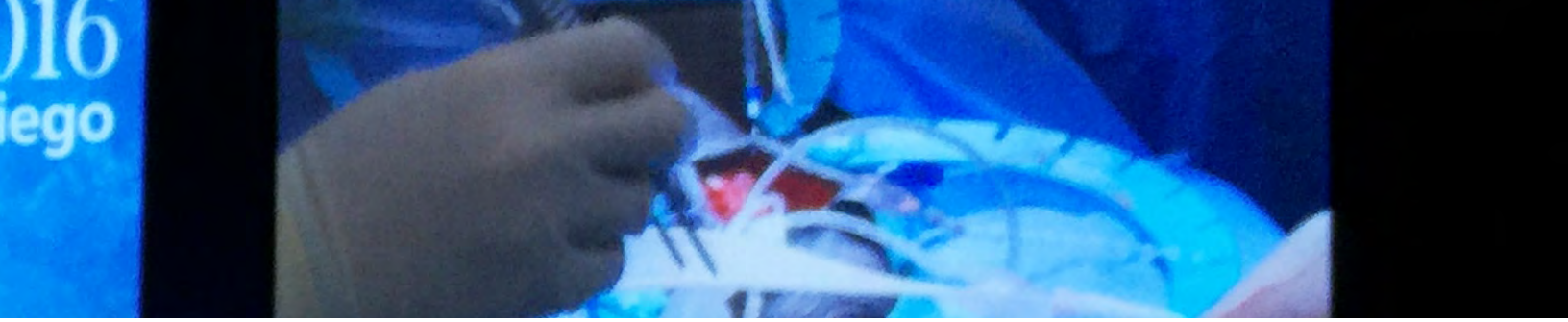
PRESENTED BY: MACK ROACH, III MD, FACR, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MOHAMMED HASEEBUDDIN, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

The Effect of Smoking on 30-Day Morbidity Following Malignancy-Related Prostatectomy

Smoking is one of the most modifiable behaviors that negatively impacts prostate cancer treatment and prevention. To determine the effect of smoking on 30-day morbidity, Dr. David Byun and colleagues conducted a secondary data analysis of patients undergoing malignancy-related prostatectomy.

Utilizing the 2005 – 2013 American College of Surgeons National Surgical Quality Improvement Program (NSQIP), 22,802 patients undergoing malignancy-related prostatectomy were identified and stratified into current smokers (12.3%), former smokers (8.2%), and never smokers (79.5%). A multivariate analysis controlled for smoking status, demographic factors and preoperative comorbidity.



As compared to former and never smokers, current smokers experienced a higher rate of total complications (p=0.05) and unplanned intubation events (p<0.001). Subsequently, multivariate analysis established current smoking status as an independent predictor of both aforementioned complication rates (total OR 1.27, 95% CI: 1.06 to 1.53, p=0.011; unplanned intubation OR 5.87, 95% CI: 2.18 to 15.8, p<0.001).

Interestingly, the same conclusions could not be made about former smoking status: total complications, unplanned intubation events and post-operative pneumonia were not found to be statistically associated with smoking beyond 12 months pre-operation.

In general, complications occur following ~5% of radical prostatectomies. Smoking status not only increases the risk for postoerative complications following radical prostatectomy, but is an independent predictor of total complications and unplanned intubation within 30 days. As recognized by the researchers, this study cannot directly pinpoint the timepoint at which the benefits of smoking cessation are incurred. However, within a context of active surveillance, clinicians could greatly benefit their patients with early counseling.

PRESENTED BY: NICK DONIN, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: LINDA HUYNH; BIOMEDICAL RESEARCH STUDENT, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Whitmore lecture—The Business of Science and the Urologic Oncologist: A Personal Journey

Dr. Arie Belldegrun, the director of UCLA Institute of Urologic Oncology, presented the 2016 Whitmore lecture. He discussed his own promising academic career. He emphasizes that a promising career for a Urologic Oncologist reaches far beyond operative room. The adventure begins with translating basic science into clinic through collaboration with and creation of pharmaceutical companies. Dr. Belldegrun stresses the importance of great mentors on shaping one's future career.

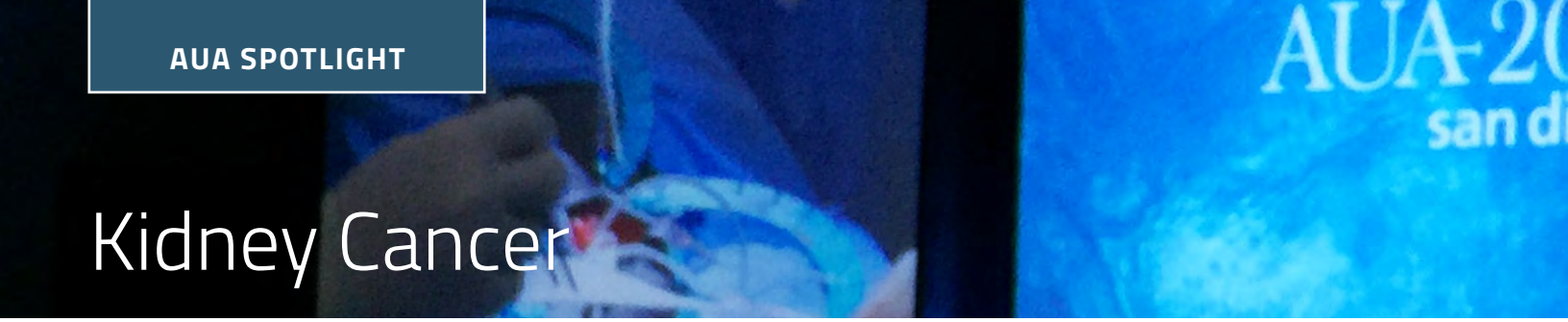
Dr. Belldegren did his residency at Brigham and then went to NCI for fellowship where he developed an interest in immunotherapy. He was fascinated with the idea that immune system can be harnessed to fight cancer. The unique experience at NCI shaped his academic career. He subsequently took an academic appointment at UCLA with a focus on immunotherapy research. He discusses that synergy in oncological research and biopharmaceutical entrepreneurship is critical. Dr. Belldegrun started a first company Agensys with his colleagues at UCLA. The group developed antibodies to several targets with various cancers. In 2007 the company was acquired by Astellas for $500 million. Dr. Belldegrun then describes the development of Xtandi. This is an example of "From OR-to-Lab-to-Clinic-And to the World" phenomenon. It involved taking samples of metastatic human prostate cancer and implanting them into mice and investigating molecular determinants of resistance to antiandrogen therapy.

The goal of the gropu was to refine and produce a safer Ketoconazole. This idea led to the creation of Zytiga. The company Cougar Biotechnology was formed. Currently UCLA is to receive > $1.14 Billion in Royalty payments from the sale of Zytiga. Dr. Belldegrun recently formed Kite Pharma. The concept is that the site of origin of cancer is not important. What is important is on the surface of immune system and search for tumor-specific antigens. The company has grown significantly over the past 2 years. Dr. Belldegrun highlights that a SUO Fellowship in Urologic Oncology should imbibe in the trainees the importance of basic science, translational science, population science, and finally the "Business of Science."

Academia is the fertile ground for scientific breakthroughs. However, Pharma is best positioned to bring products to patients. Currently, the status quo of GU malignancies has been disrupted by the introduction of new and exciting biopharmaceuticals. To stay competitive, our specialty needs to be creative beyond the clinic and OR and needs to engage in innovative science and drug development. We need to understand not only molecular pathways but also pathways for drug approval and the entire process of business of science.

PRESENTED BY: ARIE BELLDEGRUN, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MOHAMMED HASEEBUDDIN, MD; FOX CHASE CANCER CENTER, PHILADLEPHIA, PA



Kidney Cancer

Differences in Overall Survival for Patients with Stage I-II Renal Cell Carcinoma Treated with Partial or Radical

In this session, the group from Fox Chase Cancer Center looked at overall survival differences between patients undergoing partial versus radical nephrectomy for Stage 1-2 renal cell carcinoma. Retrospective studies have purported improved overall survival (OS) for patients who undergo partial nephrectomy relative to radical nephrectomy.

However, these analyses are fraught with selection biases (i.e. generally speaking, patients selected for partial nephrectomy are healthier and would therefore be expected to have better OS). The best way to eliminate such selection biases is in the context of a randomized clinical trial. In fact, we have one of those in EORTC 30904 which paradoxically demonstrated an improved OS for radical nephrectomy over partial nephrectomy in patients with renal masses 5cm and less. This study suffered from methodological flaws such as failure to accrue. In addition, when only patients with pathologically confirmed renal cell carcinoma were considered, the differences in OS were no longer significant. Other RCTs have been proposed by Campbell and Miller, however, these were shot down over concerns about the potential for adequate enrollment.

We are left then with how to account for the problems of selection bias within the context of observational studies. Two common methods of doing this are through the use of propensity score based weighting and the use of instrumental variables. These studies have been done in the Medicare population for T1a renal masses and seem to demonstrate improved initial OS for patients undergoing partial nephrectomy, though these differences are tempered over time.

Dr. Ristau and colleagues analyzed the national cancer database and utilized propensity score based weighting in an attempt to account for selection biases. 179,846 renal cell carcinomas were stratified by size into T1a and T1b/2 tumors. Increased utilization of partial nephrectomy over time for both T1a and T1b/2 tumors was seen from 2003-2012. In the entire cohort, 54.6% and 15.8% of T1a and T1b/2 masses were treated with PN Adjusted 5-year overall survival in T1a and T1b/2 for partial and radical nephrectomy were 89% and 84.6% (T1a, $p < 0.01$) and 81.3% and 80.0% (T1b/2, $p = 0.045$). The HR in favor of partial nephrectomy for T1a and T1b/2 was 0.74 (95% CI 0.71-0.76, $p < 0.001$) and 0.90 (95% CI 0.85-0.96, $p = 0.002$), respectively. When stratified by length of time after surgery and by age group, the greatest benefit for partial nephrectomy was noted in young patients with small tumors. Overall survival benefits in patients with T1b/2 tumors are tempered in comparison. In patients older than 65 years with larger tumors, PN appears to offer little OS benefit relative to RN

The authors concluded that the decision to perform partial nephrectomy in older patients with larger tumors is not straightforward and should be made in the context of competing risks and with sound clinical judgement.

PRESENTED BY: BENJAMIN T. RISTAU, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Neoadjuvant approaches to RCC perioperative immunotherapy

Dr. Harshman spoke about emerging neoadjuvant approaches to perioperative immunotherapy. In 2016, the systemic treatment armamentarium for metastatic renal cell carcinoma (mRCC) consists of 3 classes: mTor inhibitors, VEGF-targeted agents, and immunotherapy (IL-2, interferon alpha, nivolumab).

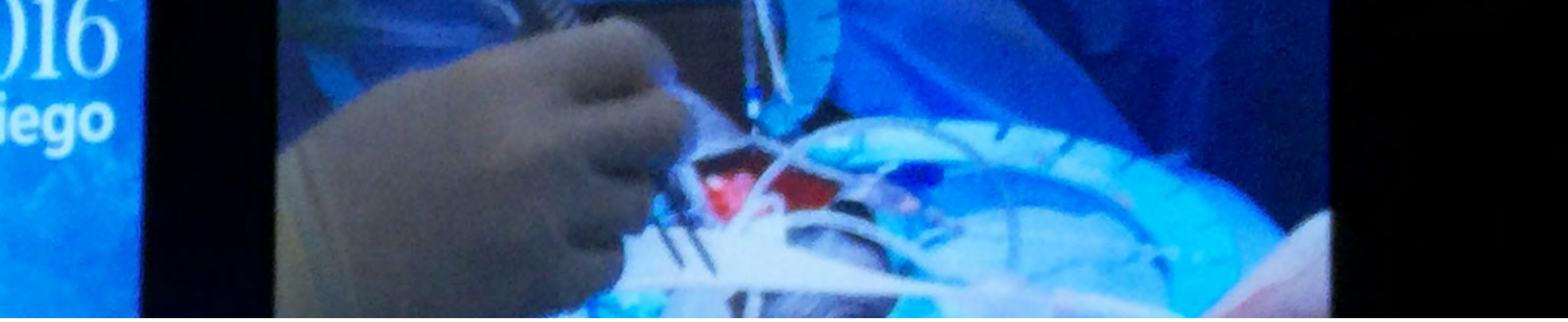
Although results from EVEREST and others are eagerly anticipated, there has been no major success using adjuvant therapies in kidney cancer to date. Therefore, Dr. Harchman argued for the next step to be moving therapy forward is in the disease process.

In the mRCC population, nivolumab demonstrated improved overall survival of 25 months versus 19.6 months compared to standard therapy (HR 0.73, $p = 0.0018$). Based on the results of this trial, nivolmab has been approved in the VEGF refractory mRCC space.

The argument to move PD-1 blockade earlier in the disease process is three-fold. (1) the durability of response can be long lasting; (2) continued response or disease stabilization occurs even off therapy (so-called "memory response"); and (3) the overall tolerability as monotherapy is high making it a good potential partner compound with other agents.

The question still remains, however, what the best treatment design would be. Namely, is it neoadjuvant, adjuvant (unlikely), or the "trifecta" of neoadjuvant-adjuvant surgical sandwich? A neoadjuvant approach brings about questions of duration and sufficient dosing for efficacy in addition to concerns about prolonged delays to curative resection. Further, the likelihood of needing combination therapy is high since monotherapy is rarely sufficient. Finally issues around which patients to select – high risk stages, PD-L1 positive only, inflammatory tumors, and mutation/immune/cytokine signatures – about making optimal trial design difficult.

Despite these challenges, there remains a strong rationale for presurgical priming. A group at Johns Hopkins University is exploring the safety and feasibility of 3 doses of neoadjuvant nivolumab followed by radical versus partial nephrectomy. The ECOG group is introducing EA81143. All patients in the study receive a renal mass biopsy. Patients are then randomized to surgery upfront followed by observation versus neoadjuvant nivolumab (2 doses) followed



by surgery followed by 9 months of adjuvant therapy. The primary outcome measure is clear cell renal cell carcinoma recurrence-free survival. The secondary endpoint is overall survival. Other outcome measures are safety, tolerability, and quality of life.

Dr. Harshman closed with imploring the audience to accept the so-called "trifecta" of presurgical priming with PD-1 blockade, surgery, and adjuvant therapy. She again reiterated earlier remarks about a complex, dynamic interplay between the tumor and the immune system. Overall, there is great hope and promise for improving care in patients with advanced renal cell carcinoma using new immunotherapeutic approaches.

PRESENTED BY: LAUREN HARSHMAN, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

REPORTED BY: BENJAMIN T. RISTAU, MD, FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Reporting Standards of Indeterminate Renal Masses on CT and MRI: A National Survey of Urologists and Radiologists by the Society of Abdominal Radiology RCC Disease-Focused Panel

Indeterminate renal masses are inherently difficult to treat, with this problem confounded by the noticeable heterogeneity between radiology reports for this type of lesion. As a result, Dr. Hu and colleagues attempted to determine the standard variables considered for an indeterminate renal mass based on a national survey of practicing radiologists and urologists.

For this study, a 35-question survey was drafted and electronically sent to consenting urologists and radiologists for completion. The SAR Disease-Focused Panel on renal cell carcinoma produced the survey for this study, which considered the possible elements of a CT/MRI report. The response rate for this study was 73% (113/154), although not all respondents answered every question.

The factors considered essential by both radiologists and urologists were size, mass type, presence of fat, presence of enhancement, size comparison to prior imaging, and radiologic staging. No consensus was found for any other elements. Compared to radiologists, urologists were significantly more likely to want the nephrometry score, yet significantly less likely to desire management recommendations on the report. In conclusion, there are specific variables essential to both urologists and radiologists when evaluating indeterminate renal masses, despite minor disagreements between the specialties.

PRESENTED BY: ERIC HU, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: AUSTIN DRYSCH; DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Could perirenal fat be more important than the tumor itself? The MAP score better predicts perioperative morbidity than the RENAL score.

The RENAL Nephrometry score is a validated tool that describes the anatomical complexity of small renal masses that has been shown to predict the complexity of various surgical procedures including partial nephrectomy. Yet, the RENAL nephrometry score only takes into account tumor characteristics such as size, depth, and location, and neglects to account for surrounding environment, such as adherent perirenal fat. It is well known that the presence of adherent perirenal fat increases the complexity of partial nephrectomy. The Mayo Adhesive Probability (MAP) score is a radiographic score that has previously been shown to aid in the prediction of adherent perirenal fat. Dr. Khene and colleagues sought to compare the predictive ability of MAP compared to the RENAL nephrometry scores for perioperative morbidity of Robot-assisted partial nephrectomy (RAPN).

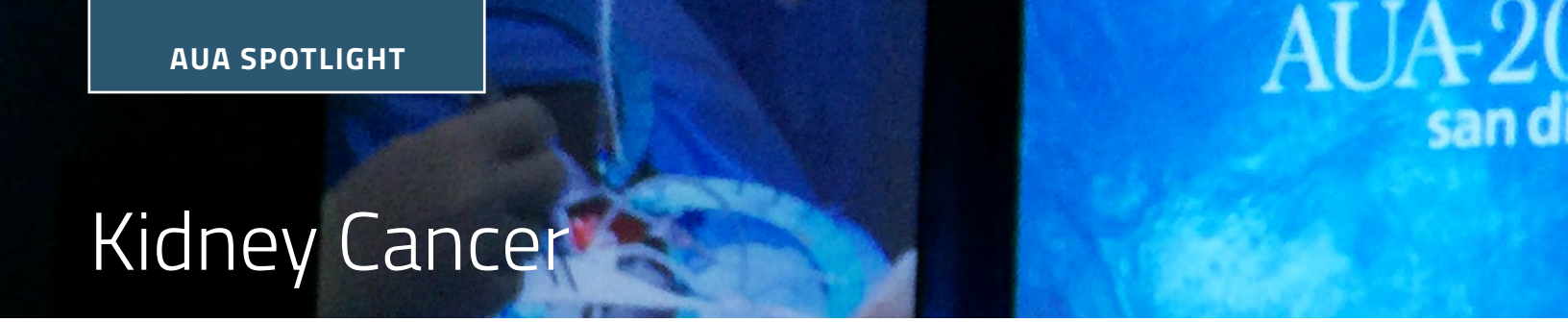
The authors conducted a retrospective review of 242 patients undergoing RAPN for small renal masses. Using routine preoperative CT images they calculated the MAP and RENAL scores and collected demographic and surgical data. They used univariate to determine variables predictive of blood loss, operative time, and risks for conversion to radical nephrectomy.

They found that both the MAP score and RENAL nephrometry score was associated with a higher rate of conversion to open surgery and the MAP score had higher predictive value (MAP OR= 4.1; 95% CI= 1.7-8.8; p=0.03 and RENAL OR 2.7 0.4-6.3 p=0.37). Both were also associated with risk of conversion to radical nephrectomy (MAP 6.1 vs. RENAL 11.4 2.1- 19.4 p=0.007). Only the MAP score was associated with risks for transfusion (MAP 2.9 1.2-4.1 p= 0.04 vs. RENAL 1.7 0.7- 2.4 p= 0.46) and operative time (beta 0.09, p< 0.001).

Thus the authors conclude the MAP score is a more useful predictive tool for anticipating operative morbidity associated with robotic-assisted partial nephrectomy. It may be easily incorporated into preoperative planning in the assessment of routine preoperative CT imaging. The authors note the limitation of using only univariate and not multivariate analysis to assess the relationship between these two scoring systems and operative outcomes.

PRESENTED BY: ZINE-EDDINE KHENE, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: SIMONE VERNEZ; UROLOGY RESEARCH FELLOW, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE



Kidney Cancer

Body Mass Index (BMI) and the clinico-pathological characteristics of localized renal masses – an international multi-institutional study

Both the incidence of obesity and renal masses have been on the rise; although obesity is an established risk factor for the development of renal cancer, its connection to histologic subtype of the tumor, prognosis, and grade remains unclear. There has been data suggesting an "obesity paradox", which is a correlation between increasing BMI and survival in patients diagnosed with renal cell carcinoma.

In order to better understand this relationship, the authors retrospectively analyzed 1,750 patients who underwent surgery for clinically localized renal masses between 2000 and 2010 at two separate institutions (one in the United States and one in Italy). Patients were grouped into four categories of Body Mass Index (BMI): A (<25), B (25-27.9), C (28-31.9), and D (≥32).

The distribution of tumor subtypes (of which clear cell was the most common) did not vary significantly by BMI group. This also held true for clinical stage distribution. However, in terms of Fuhrman grade, the proportion of low-grade (1 and 2) renal cell carcinoma was significantly higher with increasing BMI; this significant relationship also held true in subgroups stratified by gender, stage, and age.

This data is very interesting, especially when taken in the context of other recent data showing better cancer-specific and overall survival in obese patients. This study seems to support the "obesity paradox" of renal cell carcinoma with large numbers and a correlation between increasing BMI and low-grade cancer. Further study into the pathogenesis of renal cell carcinoma and its relationship to obesity and fat distribution is warranted.

PRESENTED BY: MATVEY TSIVIAN, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: RAHUL DUTTA, BS; UROLOGY FELLOW, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Reporting Standards of Indeterminate Renal Masses on CT and MRI: A National Survey of Urologists and Radiologists by the Society of Abdominal Radiology RCC Disease-Focused Panel

Indeterminate renal masses are inherently difficult to treat, with this problem confounded by the noticeable heterogeneity between radiology reports for this type of lesion. As a result, Dr. Hu and colleagues attempted to determine the standard variables considered for an indeterminate renal mass based on a national survey of practicing radiologists and urologists.

For this study, a 35-question survey was drafted and electronically sent to consenting urologists and radiologists for completion. The SAR Disease-Focused Panel on renal cell carcinoma produced the survey for this study, which considered the possible elements of a CT/MRI report. The response rate for this study was 73% (113/154), although not all respondents answered every question.

The factors considered essential by both radiologists and urologists were size, mass type, presence of fat, presence of enhancement, size comparison to prior imaging, and radiologic staging. No consensus was found for any other elements. Compared to radiologists, urologists were significantly more likely to want the nephrometry score, yet significantly less likely to desire management recommendations on the report. In conclusion, there are specific variables essential to both urologists and radiologists when evaluating indeterminate renal masses, despite minor disagreements between the specialties.

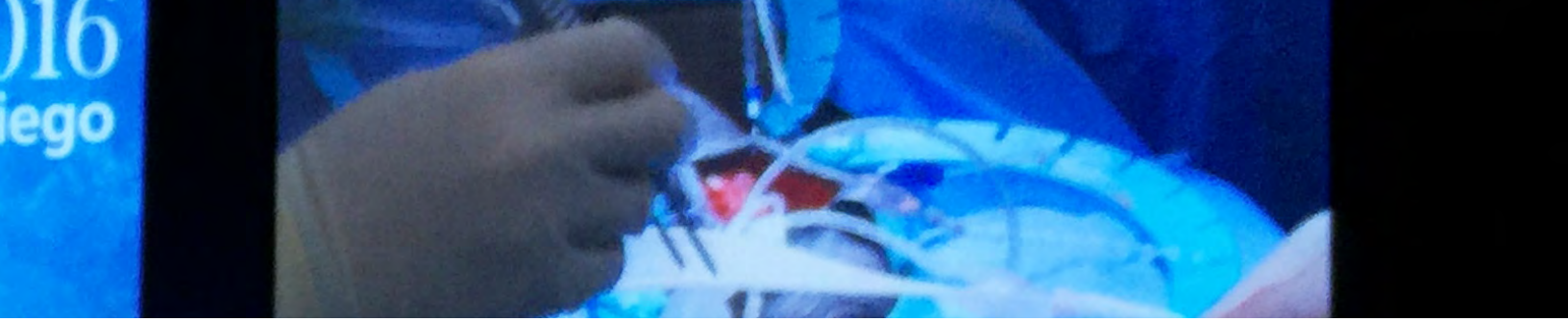
PRESENTED BY: ERIC HU, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: AUSTIN DRYSCH; DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

A Comprehensive Competing Risk Calculator For Patients With Cortical Renal Masses < 10 cm: A Novel Clinical Decision Aid For Shared Decision-Making Regarding Individualized Treatment Selection

Patients with cortical renal masses (CRM) are presented with multiple treatment options, including radical nephrectomy (RN), partial nephrectomy (PN), ablation or active surveillance (AS). The clinical tools available to assess individual risk of oncologic outcomes are limited. Dr. Psutka and colleagues aim to construct a comprehensive nomogram to estimate a 5-year cancer-specific mortality (CSM), 5-year other-cause mortality (OCM), as well as Clavien 3-5 complications (within 90-days), following treatment modalities for localized renal cell carcinoma (RCC).

In this retrospective study, the multi-institutional cohort looked at 3079 patients with localized RCC from 2000-2010, at two academic centers. They used random forest algorithms for competing risks to identify variables for the final three multivariable models. For 5-year CSM, the predicted probability for patients receiving RN, PN, ablation and AS are 12.5%, 14%, 8% and 28% respectively. For 5-year OCM, the predicted probability was 20%, 18%, 24% and 23%, respectively. Lastly, for 90-day Clavien 3-5 complications, the predicted probability for patients receiving RN, PN and ablation were 1.5%, 2.5%, and 7%, respectively.



The authors conclude that these nomograms can facilitate an easier approach to patient counseling and provide patients with estimated individualized probabilities based on basic preoperative information. At this time, they are pending external validation, and their next steps are to work with more institutions.

PRESENTED BY: SARAH PSUTKA, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: VICTOR HUYNH, CCRP; DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Limitation of Needle Deviation during Triangulated Percutaneous Renal Access: Initial Experience with a Novel Simple Device

Use of the triangulated method during a percutaneous renal access (PRA) procedure may result in unintended mediolateral deviation of the Chiba needle while under oblique fluoroscopy. To prevent this incident from occurring, Dr. Tawfik and colleagues evaluated a device aimed to stabilize the needle during the initial target of the desired caylx.

Four junior urologists completed a total of 40 PRA cases, 20 with device assistance and 20 without device assistance. The device contains a radiolucent cylinder and has a longitudinal tunnel that allows the Chiba needle to pass through. Steps during a PRA include aligning the tunnel with the desired calyx, fixing the cylinder to the patient, and monitoring the puncture while under oblique fluoroscopy. Fluoroscopic time (FT) for entering into the calyx, number of re-adjustment trials (NRATs) and complications related to access was measured.

In comparison to the cases without device-assistance, cases using the device were shown to have reduced mean FT (47 10.7 sec vs. 76.2 14.7 sec) and median NRATs (0 trials vs. 4 trials). Amongst PRA-failures, in which a mentor completed the remainder of the procedure, 5% occurred with device assistance and 25% occurred without device assistance. The authors concluded that during a triangulated PRA, the device aided junior urologists in the stabilization of the Chiba needle and minimized or completely eliminated the occurrence of mediolateral deviation while targeting the calyx.

PRESENTED BY: AHMAD TAWFIK, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BRITTANY URIBE, BS; JUNIOR SPECIALIST, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Findings and Impact of Early Imaging Following Partial Nephrectomy

Currently, AUA guidelines for the surveillance of patients treated with partial nephrectomy for renal cell malignancies recommend follow-up imaging within 3 to 12 months post-op. However, some expected post-operative changes can be difficult to interpret and lead to abnormal imaging. This can in turn lead to increased patient anxiety regarding their results, as well as uncertainty for the urologist. To evaluate this hypothesis, Dr. Tubre and colleagues performed a retrospective review of partial nephrectomy cases at their institution and they presented their finding in their podium presentation. Their objectives for this study were to examine if abnormal findings are associated with earlier post-operative imaging and if it also leads to earlier additional imaging or an increase in the rate of earlier detection of recurrence.

From 2006 to 2013, the authors reported a total of 180 partial nephrectomy cases with a minimum of 2 years of follow-up imaging. Approximately, 70% of the total patients were considered to have normal findings in their initial post-op images and approximately 30% were considered to be abnormal at initial post-op images.

Of the abnormal imaging group, 60% were deemed normal on subsequent imaging. Significant differences were observed for median time initial follow-up for normal vs abnormal imaging (205 vs 133 days) and the median time interval between imaging (188 vs 157 days).

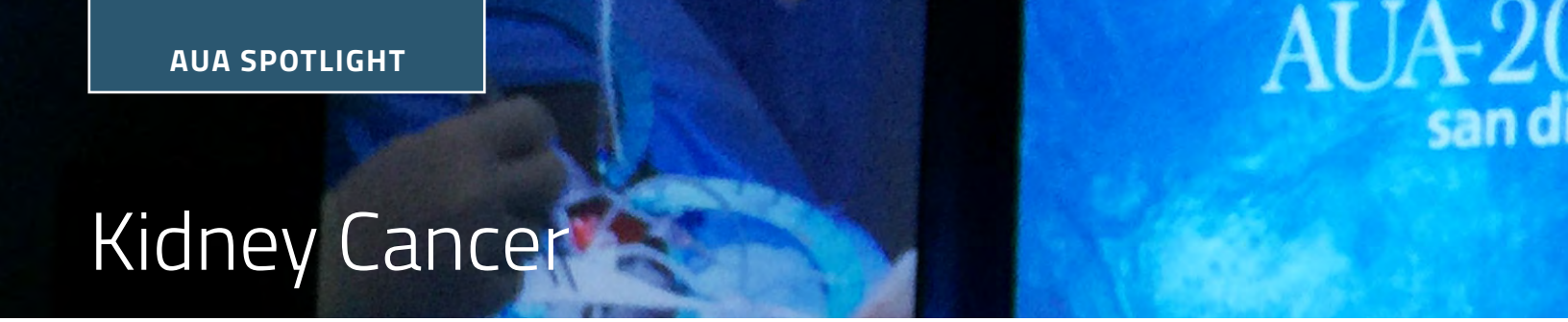
Their results of this review revealed that imaging obtained prior to 6 months post-op resulted in more abnormal findings than images obtained more than 6 months post-op. Overall, this led to closer follow-up and earlier repeat imaging but there was no increase in the rate of recurrence detection. The authors concluded from their findings that post-operative imaging can potentially be delayed up to 1 year after surgery to reduce the number of unnecessary additional imaging as well as patient anxiety due to their indeterminate imaging.

PRESENTED BY: RYAN TUBRE, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: RENAI YOON; RESEARCH ASSOCIATE, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Long-term 10-year health-related quality of life outcomes following radical cystectomy

Nearly 7,000 patients undergo radical cystectomy (RC) with urinary diversion in the United States each year. Though RC improves mortality, it is associated with significant morbidity, especially with regards to bladder, bowel and sexual function. Ileal conduit



Kidney Cancer

(continued from page 37)

(IC), neobladder (NB) and Indiana pouch (IP) urinary diversions are all offered after radical cystectomy and the literature is conflicting regarding the optimal method of urinary diversion.

Further, most quality of life studies comparing various diversion types are relatively short- term, less than 12 months. Dr. Gellhaus and colleagues sought to evaluate health- related quality of life following radical cystectomy with urinary diversion by IC, NB and IP in a large cohort with long-term (greater than 10 year) follow- up.

The authors performed a retrospective review of a single- institution radical cystectomy database. They identified 300 living patients with greater than 5 years follow up and sent the validated, disease specific health- related quality of life survey, the Bladder Cancer Index (BCI) instrument. ANOVA analysis was used to compare baseline characteristics and ANCOVA was used to adjust for age, gender, surgeon, age at time of surgery, and total follow up time. A separate sub- analysis of patients with <65 and >65 years was conducted.

28 patients (42.7%) completed the BCI survey. Urinary function was better for patients with IC and IP (p= 0.0002). IP had lower sexual function scores relative to IC and NB (p= 0.0387). Age stratification revealed some differences in males, with urinary function better in males >65 years who received an IC (p= 0.0086). Urinary function was better in males <65 with IC and UP than NB (p=0.0074). In females >65 years, bowel bother and function were significantly better for IC than for IP (p= 0.0453 and p= 0.0168).

This represents a unique study with long- term follow up in patients with three types of urinary diversion, including the largest group of patients undergoing urinary diversion with an Indiana pouch. The authors conclude that type of urinary diversion significantly affects health related quality of life outcomes after radical cystectomy. Quality of life outcomes were significantly different according to gender and age at surgery.

PRESENTED BY: PAUL GELLHAU, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: SIMONE VERNEZ; MEDICAL STUDENT, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

B-lymphocytes differentiation is atypical in clear cell renal cell carcinoma (ccRCC) and low preoperative B-cell count is associated with poor cancer specific survival (CSS)

B-lymphocytes are important antigen-presenting cells. There are several reports in the literature on the association of ccRCC and lymphoma of B cell origin. Therefore, the group theorized that B-cells may be atypically distributed in ccRCC and may be associated with poor outcomes.

Blood samples were obtained from RCC patients before partial or radical nephrectomy and age-similar non-cancer controls. Flow cytometry was performed and data was quantified as mean fluorescence intensity (MFI) or % cells that express a biomarker. Patients were excluded if they had comorbid CLL, prior surgeries for RCC, non-ccRCC histology. B-cells were defined as CD45+/CD19+ and further characterized with other markers. Low B-cell count was defined to be below the first quartile level (141 cells/µl) in the healthy donors.

ccRCC patients and healthy donors had similar distributions of BL count [median 170/µl (28-679) vs. 189/µl (83-408), p = 0.49]. With median follow-up of 41 months (1-55 mo), 10 patients died with ccRCC. Patients with BL < 141/µl had lower CSS compared to patients with BL > 141/µl (p = 0.0013). This was seen in also in otherwise localized ccRCC patients. In a multivariable analysis, this was significant with adjustment for T-stage and non-localized disease. Compared to healthy non-cancer controls, B-lymphocytes in ccRCC had higher percentages of CD27+ phenotype and lower percentages of CD20% cells.

The group concludes that in patients with ccRCC, low B-lymphocytes is prognostic of poor cancer survival. Furthermore, B-lymphocytes are atypically differentiated compared to non-cancer healthy controls.

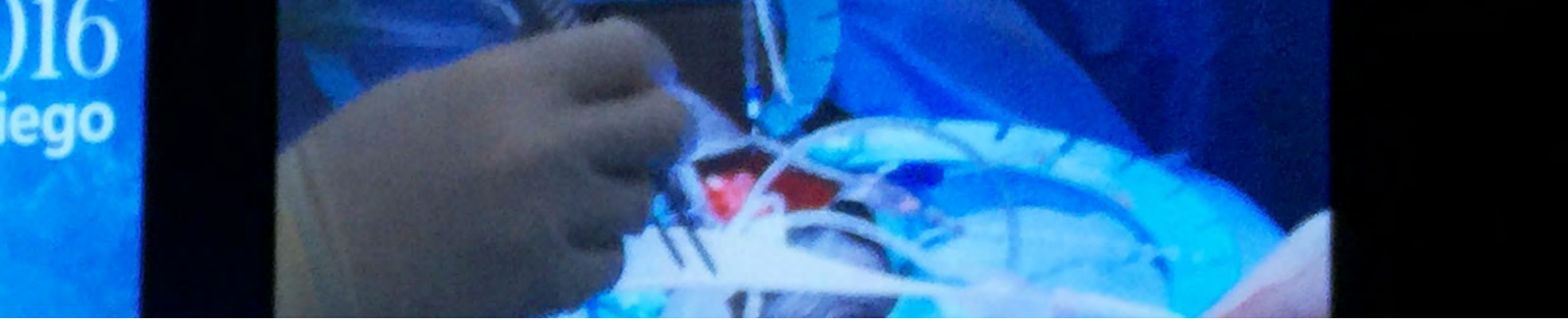
PRESENTED BY: MOHAMMED HASEEBUDDIN, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MOHAMMED HASEEBUDDIN, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Spectrum of radiological findings of hereditary leiomyomatosis and renal cell cancer (HLRCC)

Individuals with hereditary leiomymatosis (smooth muscle tumors) have a 15% lifetime risk of developing renal cell carcinoma, and thus are of special interest in the urological field. Small aggressive papillary carcinoma type II tumors with an increased metastatic potential are the typical tumors classified under hereditary leiomyomatosis and renal cell cancer (HLRCC). In this study, the authors sought to classify the heterogeneous imaging nature of HLRCC in order to improve screening and diagnosis.

HLRCC lesions from a total of 30 patients were evaluated with CT and/or MR for cystic, enhancement, homogeneity, heterogeneity, nodules/septations, margin definition, and maximal axial diameter. On CT three distinct categories of lesions were classified: 53% of lesions were found to be heterogeneous cystic, 35% were found to be heterogeneous solid, and 12% were found to be homogenous solid. On MRI, the homogenous solid lesions were found to be small



(2.4cm), appear hypo-intense on T2 imaging and non-hemorraghic. Heterogenous cyst and heterogeneous solid lesions tended to be larger (4.5cm and 6.7cm, respectively), appear hyper-intense on T2, and be hemorraghic. All three lesions were associated with metastasis and with a restricted diffusion feature.

Although highly varied in size and appearance, HLRCC manifests as heterogenous lesions with cystic and solid components. The authors stress the importance of a thorough family history for identification possible ties to HLRCC since 80% of patients will present with cutaneous or uterine leiomymatosis. In addition, continuous careful screening of even small lesions to monitor for changes in appearance in light of the high metastatic potential of HLRCC.

PRESENTED BY: JANA LOVELL, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BLANCA MORALES; DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Renal function before and after cytoreductive nephrectomy in a phase 3 randomized clinical trial

Erik Mayer's group explored the impact of cytoreductive nephrectomy (CN) on renal function and ae presenting this here. They assessed patients in the Autologous Dendritic Cell Immunotherapy Plus Standard Treatment of Advanced Renal Cell Carcinoma (ADAPT) trial, a vaccine based immunotherapy trial. The objective of the present study was to assess renal function before and after CN in this patient population.

Renal function before and after CN was determined using the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Calculator. A retrospective review of prospective collected data from January 2013 through January 2015 was performed for tumor characteristics, established chronic kidney disease (CKD) risk factors, and demographic information. Univariate and multivariate logistic regression analyses were used to evaluate the impact patient and disease-specific factors on pre-operative renal function.

Of 1007 patient for whom preoperative renal function data were available, 198 (19.7%) had CKD ≥ 3 (GFR < 60ml/min/1.73m2). Age at diagnosis (OR 1.064, 95% CI: 1.042-1.087), LDH above the upper limit of normal (OR 1.851, 95% CI: 1.231-2.781), and advanced tumor stage were independent predictors of postoperative CKD ≥ 3. At the time of surgery, the likelihood of having at least CKD 3 was lower for T1 (OR 0.432, 95% CI: 0.192-0.969) and T2 (OR 0.303, 95% CI: 0.117-0.788) than for T3 tumors. Gender, race, low albumin, symptomatic metastasis, and positive lymph nodes were not significantly associated with CKD ≥ 3.

Post-operative GFR data was only available for 426 patients. The median change after CN was a loss of 21.6ml/min/1.73m2. Of the patients available for analysis, 160 (37.6%) developed CKD ≥ 3 post-CN in the setting of previously normal renal function.

Mr. Mayer concluded that 20% of patients with mRCC in the ADAPT trial have baseline CKD ≥ 3 and nearly 40% with previously normal renal function develop CKD ≥ 3 after CN. Moreover, patients who are older and who have more advanced disease may be at higher risk of significant renal insufficiency after CN. These data can be used to council patients preoperatively regarding their risk of post-CN de novo renal insufficiency.

The full study design for ADAPT can be found at https://clinicaltrials.gov/ct2/show/NCT01582672?term=AGS-003&rank=2.

PRESENTED BY: ERIK N. MAYER, BS AT THE 2016 AUA ANNUAL MEETING – MAY 6 - 10, 2016 – SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD, FOX CHASE CANCER CENTER, PHILADELPHIA, PA

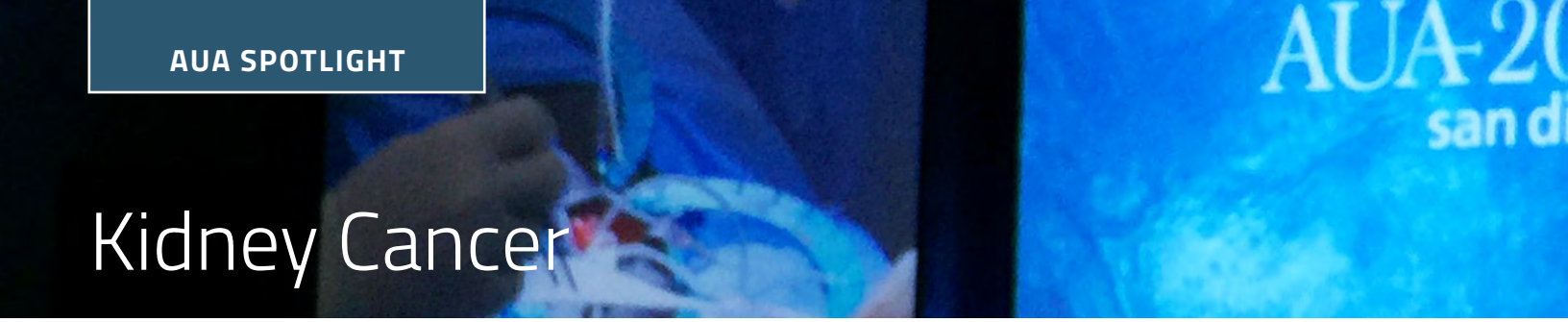
Optimization of Surveillance Following Nephrectomy for RCC?

Dr. Miller spoke about optimization of surveillance following nephrectomy for renal cell carcinoma (RCC). The 2016 AUA and NCCN guidelines currently stratify patients by stage with low risk patients recommended to receive imaging for 3 years' duration and higher risk patients getting 5 years of postoperative imaging. After these time points, further screening is up to the discretion of the ordering physician.

Despite these guidelines, the effectiveness of capturing RCC recurrence is unclear with up to 1/3 of all recurrences missed when AUA/NCCN guidelines were used. Further the AUA and NCCN follow-up guidelines fail to account for change in recurrence risk over time, influence of competing risks to mortality, RCC recurrences that occur after 5 years, and the economic burden of follow-up imaging on the health care system which has been estimated to approach $13,000 per patient.

Some barriers to surveillance optimization include an uncertain impact of postoperative imaging on survival and influences of lead-time bias. Even still, surveillance continues to be fundamental to RCC care due to its perceived benefits. Proponents argue the utility of postoperative imaging may include detection of post op complications (e.g. renal failure), the ability to capture recurrences early leading to more options for therapy, and advancements in targeted therapy generating favorable impacts on survival.

Dr. Miller then argued for a restructuring of RCC surveillance. A sophisticated surveillance algorithm ought to move beyond TNM staging and include more features leading to more individualized strategies. She did warn, however, that if surveillance models



Kidney Cancer

(continued from page 39)

become overly complicated and burdensome, underutilization and heterogeneous care will be perpetuated.

The current framework for postoperative imaging uses linear calculation. Instead of a simply stage-based risk stratification scheme, Dr. Miller argued for a transition time point away from rigorous identification of recurrent disease at the point where competing health risks exceed the risk of RCC recurrence. She proposed Weibull modeling which captures the dynamic interaction between risk of RCC recurrence and risk of non-RCC death, thereby identifying key transition time points.

Lastly, these models require external validation to verify their effectiveness as well as outcome assessment (including patient reported outcomes) to compare new algorithms to current frameworks

Dr. Miller closed by noting that the current surveillance framework merits optimization, which can be done by restructuring surveillance and developing more sophisticated algorithms.

PRESENTED BY: SUZANNE B. MILLER, MD AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Identifying mRCC Patients with Venous Thrombus Who Are Likely to Benefit from Cytoreductive Surgery

In this session, Dr. Abel presented his work looking at the ability to predict poor overall survival in patients with metastatic renal cell carcinoma (mRCC) and tumor thrombus. The objective of the study was to determine which patients would be least likely to benefit from cytoreductive nephrectomy (CN) due short post-operative survival.

This was a retrospective multi-institutional (4 centers) analysis of consecutive patients with mRCC and venous thrombus at presentation treated with upfront CN from 2000-2014. Prognostic systems from Memorial Sloan Kettering Cancer Center (MSKCC), international metastatic database consortium (IMDC), and MD Anderson Cancer Center (MDACC) were used to classify patients. Kaplan Meier analysis was used to estimate overall survival (OS). Univariate and multivariable Cox proportional hazard models were used to evaluate the association of individual variables with OS.

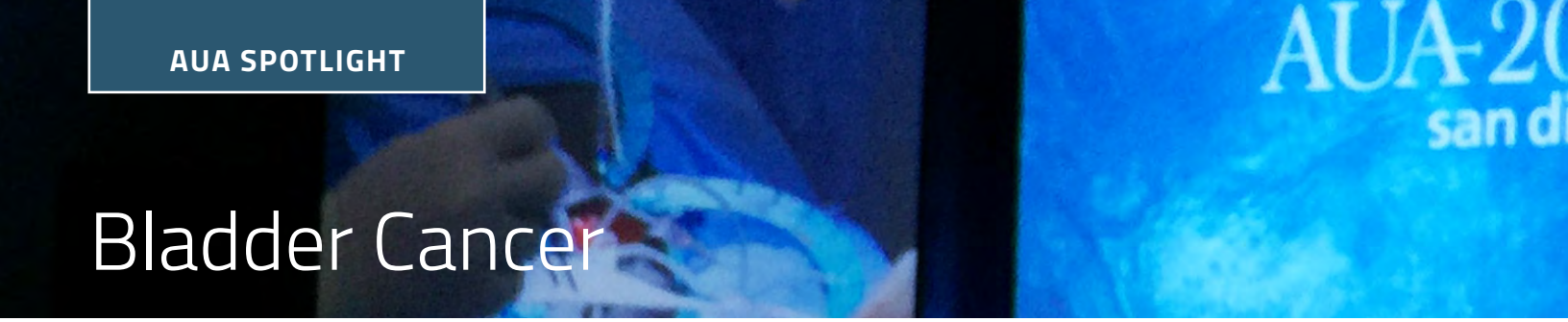
Overall survival for the entire cohort (n=293) was 17.2 (IQR 6.4-41) months. Venous thrombus level as determined by the Neves system was 0, 1, 2, 3, and 4 for 77, 38, 104, 45, and 29 patients, respectively. Median OS was worse for patients with IVC thrombus above the diaphragm compared to renal vein only thrombus or IVC thrombus below the diaphragm (6.8, IQR 2.2-19.1 months versus 18.8, IQR 8.1-37.8 months versus 18.9, IQR 6.7-44.5 months, respectively; p = 0.03).

Risk group stratification was used to compare the ability of systems to predict short OS. MSKCC poor risk patients had median OS 13.4 (IQR 4.4-28.2) months, IMDC poor risk patients had median OS 12.5 (IQR 5-35) months, and MDACC unfavorable risk patients had median OS 6 (IQR 4-28.2) months. Independent predictors of poor OS included tumor thrombus above the diaphragm (HR 5.2, 95%CI: 2.4-11.3), serum lactate dehydrogenase greater than upper limit of normal (HR 1.7, 95% CI: 1.1-2.6), and systemic symptoms (HR 2.2, 95% CI: 1.4-3.3).

Dr. Abel concluded that patients with mRCC and tumor thrombus classified as unfavorable risk using the MDACC criteria have poor OS and may not benefit from cytoreductive nephrectomy and thrombectomy.

PRESENTED BY: E. JASON ABEL, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA



Bladder Cancer

Anti-PDL and anti-PDL-1 trials in bladder cancer

In this session, Dr. Vogelzang reminded the audience that advanced UC is uniformly fatal after failure of platinum chemotherapy. Durable response is rarely seen and the Median survival is 9.2 (5.7-11.7) months. To make matters worse, grade 3-4 toxicities are high.

Enter immune checkpoint blockade and the PD-1/PD-L1 pathway. PD-1 is a negative costimulatory receptor expressed primarily on activated T cells. PD-L1 is broadly expressed in human cancer. Specific subgroups harbor high levels of PD-L1. For example, lynch syndrome patients are hypermutated and demonstrate corresponding hypersensitivity to immune checkpoint inhibitors.

Dr. Vogelzang highlighted the IMvigor 210 trial, which includes patients with mUC whose tumors are PD-L1 positive and have progression during/following platinum-based first line chemotherapy. PD-L1 positivity is determined based on 3 scoring levels: IC2/3 (≥5%), IC1 (≥1 but <5), and IC0 <1%). They receive atezolizumab 1200mg IV every 3 weeks until loss of benefit. The co-primary endpoints are overall response rates (ORR) by RECIST v1.1 criteria and ORR per investigator-assessed modified RECIST criteria. Key secondary endpoint are duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

A total of 310 patients were evaluated. Median age was 66 years, 78% of patients were male, 74% had a bladder primary, and 37% had prior cystectomy. PD-L1 status was 32%, 35%, and 33% for IC2/3, IC1, and IC0, respectively. ORR for all comers was 15% (95%CI 11-19%). Though responses were seen in all PD-L1 subgroups, greater ORR was associated with higher PD-L1 IHC status. Complete responses (CR) were seen in 5% of all comers and up to 11% in patients with IC2/3. Responses were durable and the median DOR (range 2-13.7 months) was not reached in any PD-L1 subgroup at median follow-up of 11.7 months (range 0.2-15.2 months). Ongoing responses were seen in 38/45 (84%) responding patients. The disease control rate (defined as CR+partial response+stable disease) was 35%, 21%, and 19% for IC2/3, IC1, and IC0 IHC subgroups, respectively. Median PFS was 2.1 months for all patients and 6-month PFS occurred in 30%, 17%, and 21% of IC2/3, IC1, and IC0 IHC subgroups, respectively. The 12-month OS was 48%, 30%, and 36% for IC2/3, IC1, and IC0 IHC subgroups, respectively. This compares favorably with estimates of 20% 12-month OS for patients in a second line only setting (Agarwal N et al., Clin Genitourin Cancer 2014). The safety profile was acceptable with only 11% of patients reporting serious adverse events (AEs) and no deaths attributable to therapy. The AE profile was similar across IHC groups.

Generally speaking, Dr. Vogelzang highlighted that a higher response was seen in high immune PD-L1 expressing patients and vice versa. However, this was not exclusive and demonstrated the highly dynamic nature of immune checkpoint inhibition. Heavy pre-treatment did not preclude response and the most likely people to respond were lymph node only metastatic sites (relative to hepatic).

Responses were durable, but benefit should not be confined to response as many patients experienced disease stabilization. The overall response rate was highest in patients with a high mutational load and also in those the cluster 2 luminal TCGA sub-types. The authors concluded that "Although PDL1 immune cell status is clearly associated with atezolizumab response, incorporation of TCGA gene expression subtype, mutational load, or both of these novel biomarkers…will allow the formal construction of…a next generation of companion diagnostics" (Rosenberg et al. Lancet 2016; 387: 1909).

Dr. Vogelzang concluded that these molecules have the potential to change the trajectory of the natural history of urothelial carcinoma both in localized and metastatic disease. Further, the toxicity of the antibodies is low and can be given to patients with significant renal dysfunction. More study needs to be completed around response prediction, duration of response, and resistance. Finally, studies combining agents with other anti-neoplastic agents is a high priority for urological oncology research.

PRESENTED BY: NICHOLAS VOGELZANG, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD; USA FOX CHASE CANCER CENTER, PHILADELPHIA, PA

What To Do With BCG Refractory NMIBC When Cystectomy is Not an Option

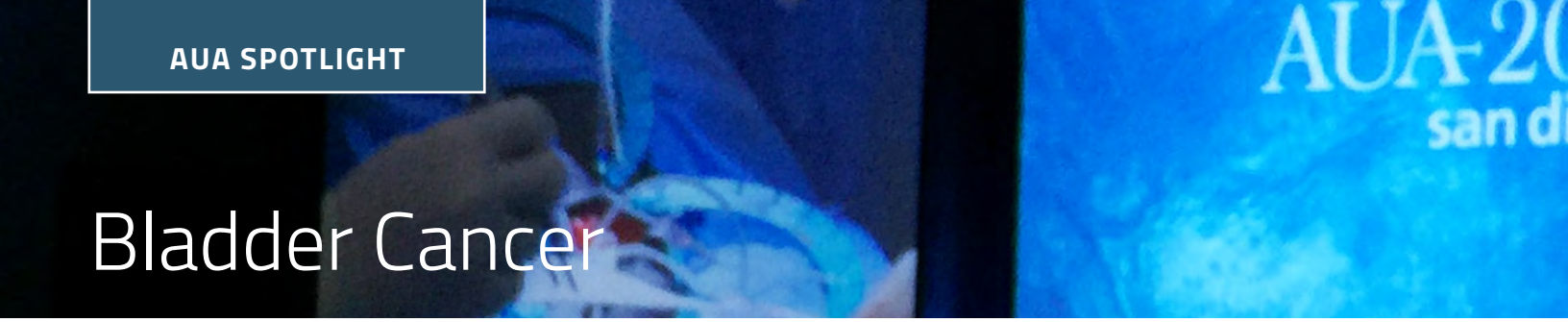
Dr. Cookson gave an overview on the management of BCG refractory NMIBC. BCG has been shown to be a standard for most intermediate and all high-risk NMIBC. It is superior to intravesical chemotherapy and has been endorsed by multiple international guidelines. The efficacy is best with maintenance therapy. SWOG 8507 trial illustrates a 2-year recurrence free survival (RFS) of 82% vs 62% with and without maintenance respectively.

Despite the benefits of BCG, long-term disease free and progression free survival is difficult to achieve. Up to 50% with high risk NMIBC will recur after BCG therapy. Risk of progression also increases with each round of failed therapy. Disease progression can be lethal and effective salvage therapy is needed. Potential causes of BCG failure are host immune incompetence, inadequate resection, resistant or non-antigenic tumor, inadequate treatment schedule inadequate dose, inadequate contact of BCG and excess BCG inducing immunosuppression.

Definitions of BCG failure are critical:

1. Intolerant: recurrent disease in setting of inadequate BCG dose due to side-effects.

2. Resistant: recurrence of or improving disease that resolves with further BCG.



Bladder Cancer

(continued from page 47)

3. Relapsing: recurrence after achieving 6 month of complete relapse.

4. Refractory: No complete relapse by 6 months after BCG. Not improving or worsening disease despite two courses of BCG or maintenance.

Six months is the treatment period to identify high-risk tumors as truly refractory. While anatomic definition of refractory state is the standard, the group from MD Anderson is investigating a molecular definition of failure using FISH assays.

Cystectomy has a high rate of cure in BCG refractory NMIBC but before progression to muscle invasion. However, morbidity remains high and not all patients are candidates for cystectomy.

Valrubicin is approved by FDA as an intravesical therapy in patients who are BCG refractory. While initial results were exciting (32% complete relapse at 6 months), late results were not so much (only 8% remained NED at 30 months). This highlights the need for additional bladder-conserving therapies.

Other modalities that are under investigation are intravesical Gemcitabine, Taxane, and BCG + IFN. Hyperthermia Synergy is also being investigated. It involves delivery of hyperthermic chemotherapy with temperatures of 41 to 44 degree Celcius. It is thought that this would lead to direct cytotoxic effect and enhanced penetration of chemotherapy agent. Photodynamic Therapy and checkpoint inhibitors are also under investigation.

Dr. Cookson concludes that clinical BCG failure is now better defined. Cystectomy is the standard of care. Best salvage therapy is yet to be defined. Single agent chemotherapy has modest complete response and best results are seen with maintenance. In future, we need to develop molecular tools to predict response or failure, better surgical strategies to eradicate CIS, and a personalized therapy tailored to individual patient and tumor risk profiles.

PRESENTED BY: MICHAEL S. COOKSON , MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MOHAMMED HASEEBUDDIN, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

The Optimal Antibiotic Prophylaxis for Radical Cystectomy: a population-based analysis

In this session, Dr. Krasnow and colleagues from the Brigham and Women's Hospital presented work looking at the optimal antibiotic prophylaxis regimen in patients undergoing radical cystectomy. The objective of the study was to examine variability in antimicrobial prophylaxis and which regimen resulted in the fewest infectious, soft tissue, and wound related events (ISWE).

The premier prospective database was used for the present analysis and captured patients undergoing radical cystectomy from 2003-2013 for whom perioperative antibiotic prophylaxis information was available. The primary outcome was ISWE, which were defined using the Agency for Healthcare Research (AHRQ) Clinical Classification Software. Secondary outcomes were infectious events in the absence of soft tissue, soft tissue and wound only events, and length of stay.

The authors demonstrated a large amount of variability regarding antimicrobial prophylaxis in patients undergoing radical cystectomy. Only about 28% adherence to guideline was noted. The regimen with the best outcomes was combination therapy with 1st generation cephalosporin or penicillin with an aminoglycoside or 2nd/3rd generation cephalosporin. The optimal antibiotic regimen and duration should be further studied to optimize perioperative ISWE

PRESENTED BY: ROSS KRASNOW, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

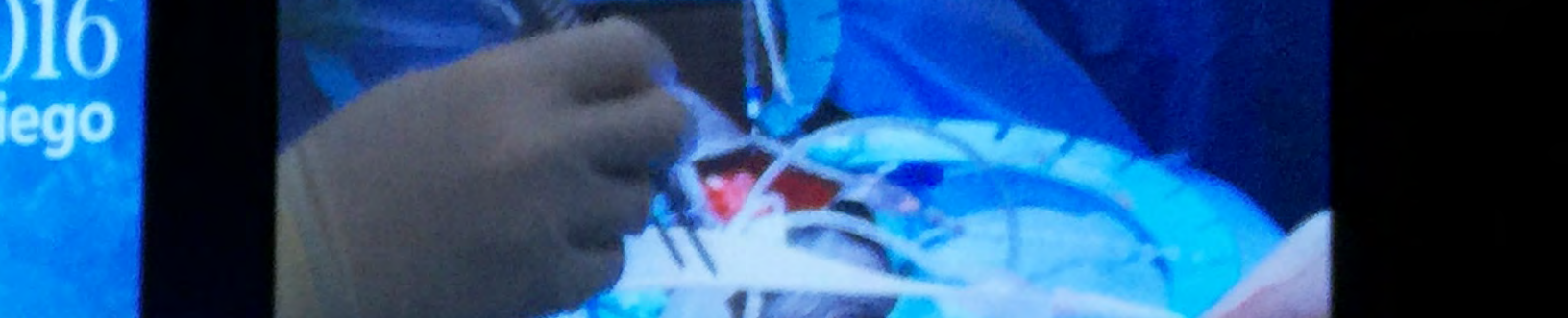
WRITTEN BY: BENJAMIN T. RISTAU, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

A Phase I/II Trial of Prehabilitation in Patients Undergoing Cystectomy for Bladder Cancer

In this session, Dr. Montgomery and the group from Ann Arbor presented the interim results of a phase 1-2 study looking at prehabilitation (i.e. rehabilitation prior to any intervention) for patients with muscle-invasive bladder cancer undergoing radical cystectomy. Patients greater than 60 years old were asked to exercise in a 1:1 supervised setting with a certified personal trainer 3 times per week for 4 weeks before surgery. Fitness and quality of life (QOL) measures were obtained at baseline and after completing the exercise course. QOL was reevaluated at 30 and 90 days after surgery.

Twenty-two patients with mean age 71.8 years and median Charlson comorbidity index (CCI) of 6 were included. Patients were able to attend approximately 75% of all exercise sessions and there were no adverse events. Mean length of hospital stay was 7.1 days. Ninety-day readmission and any complication rates were 36.1% and 73.1%, respectively. Compared to baseline levels, patients improved their 15-foot walk test by 20 seconds, 6-minute walk distance by 53 feet, and submaximal exercise test VO2 by 1.7ml/kg/min. Relative to baseline, normative SF-36 scores improved for the physical general health, vitality, mental health, and physical composite score domains. Pysical and vitality domain scores decreased after surgery, but returned to baseline by day 90. General health and mental health scores improved throughout the duration of the study.

The authors concluded that prehabilitation in cystectomy patients is feasible, safe, and results in improvement in fitness and endurance



parameters. Complication and readmission rates unfortunately remain high despite prehabilitation. Further recruitment to this study is ongoing.

PRESENTED BY: JEFFREY MONTGOMERY, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Progression from Non-Muscle Invasive Bladder Cancer (NMIBC) to Muscle Invasion is Associated with Lower Response Rates to Neoadjuvant Chemotherapy

The use of neoadjuvant chemotherapy for bladder cancer has shown positive results in past studies; however, no studies have been performed to determine if bladder cancer patients that progressed from non-muscle to muscle invasive bladder cancer respond different to this therapy compared to patients with de novo muscle invasive bladder cancer. To evaluate this concept, Dr. Pietzak and colleagues performed a retrospective review of patients with clinical stage T2-4aN0M0 urothelial muscle invasive bladder cancer treated with 3-4 cycles of cisplatin-based NAC followed by radical cystectomy and presented their findings.

Of patients from 2001 to 2015, the authors reported a total of 288 patients of which 85% had de novo muscle invasive bladder cancer. Clinical variables such as pathologic response rates after neoadjuvant chemotherapy, overall survival, cancer-specific survival, and recurrence-free survival were evaluated.

Their results of this retrospective study revealed that patients that progressed from non-muscle to muscle invasive bladder cancer had significantly lower pathologic response rate after neoadjuvant therapy but significantly worse overall survival, recurrence-free survival, and cancer specific survival compared to patients with de novo muscle invasive bladder cancer. However this result was not longer significant after adjusting for pathologic T stage. Overall, patients that progressed from non-muscle to muscle invasive bladder cancer were still associated with increased risk of recurrence. The authors concluded from their findings that these patients appear less likely to respond to neoadjuvant therapy compared to patients with de novo muscle invasive bladder cancer

PRESENTED BY: EUGENE PIETZAK, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: RENAI YOON; RESEARCH ASSOCIATE, DEPARTMENT OF UROLOGY, UNIVERSITY OF CALIFORNIA, IRVINE

Impact of lymph node dissection at the time of radical nephrectomy and tumor thrombectomy on oncological outcomes of patients with renal cell carcinoma and tumor thrombus

In this session, Dr. Chandrasekar and colleagues sought to analyze the impact of lymph node dissection at the time of nephrectomy and tumor thrombectomy on oncologic outcomes in patients with renal cell carcinoma and tumor thrombus. The records of 1978 patients from 24 centers with RCC and tumor thrombus and without evidence of systemic metastasis were included. All patients underwent radical nephrectomy with tumor thrombectomy between 1985-2014. The primary outcome measure was 5-year cancer-specific survival (CSS) and multivariable analysis was performed to identify independent predictors of CSS.

The overall 5-year CSS was 60.9% (95% CI 58.1-63.5%). Lymphadenectomy was performed in 1026 patients and lymph node (LN) metastasis was seen in 223 (21.7%). The median number of LNs removed was 7 and patients with LN metastases had a median of 2 positive LNs. On multivariable analysis, the presence of LN metastasis, number of positive LNs, and LN density were independently associated with cancer-specific mortality.

Clinical node negative disease was documented in 573 patients and 43 (10.6%) of these patients had pathologically positive lymph nodes at surgery. Patients with clinical node negative and positive nodes at surgery demonstrated improved CSS compared to patients with clinically and pathologically positive nodes (3-year CSS 50.2% versus 33.7%, p =0.047). In multivariable analysis for patients in this subgroup, positive clinical node status was an independent predictor of cancer specific mortality (HR 2.923, p=0.015).

The authors concluded that number of positive LNs and LN density were strong prognostic indicators of better CSS. They also noted that the rate of pathologically positive LNs among clinically negative LN patients is high. Therefore, they argued that a lymphadenectomy should be routinely done in this challenging patient population.

PRESENTED BY: THENAPPAN CHANDRASEKAR, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: BENJAMIN T. RISTAU, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Penile and Testicular Cancer

Prognostic and pathologic factors determining outcomes in pT2/pT3 penile carcinomas: Time for a revised staging system

A very interesting podium presentation was presented at the AUA 2016 conference on today's sexual Function/Dysfunction: Penis/Testis/Urethra: Benign Disease & Malignant Disease that described Prognostic and pathologic factors determining outcomes in pT2/pT3 penile carcinomas: Time for a revised staging system.

Dr. Priya Rao reminded all that Tumors invading corpus spongiosum (CS) and/or corpora cavernosa (CC) are currently staged as pT2 tumors. The authors sought to assess the 7th edition TNM pathologic staging system for penile carcinoma and define the pathologic prognostic factors that determine clinical outcome. The study included 147 pts from 2 cancer institutes, who had radical penectomies between June 1999 & May 2013. The patients were divided into 4 groups:

Group1: CS involvement without LVI (N= 41)

Group2: CS involvement with LVI (n=42)

Group3: CC involvement (n=29)

Group4: Urethra involvement (n=35).

Overall and disease specific survival were estimated using the Kaplan-Meier method, and two-sided log-rank tests & Cox proportional hazards regression models adjusting for histologic grade. Median was 5.1 years. the authors found that overall survival was significantly associated with tumor grade ($p<0.001$) and pathologic group ($p=0.003$). Median disease specific survival was 1.5 years. On multivariate analysis DFS was significantly associated with pathologic group only. The authors showed that there is a significant statistical difference in OS and DFS when tumors currently classified as pT2/pT3 tumors are stratified into 4 groups. OS for tumors involving the CC is significantly worse than tumors involving the CS, behave similarly to tumors showing urethral involvement, thus warranting a separate T category. Furthermore, tumor grade did not significantly impact DFS in pT2 tumors, which was impacted by pathologic group alone.

PRESENTED BY: PRIYA RAO, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MIKI HAIFLER, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Immune Profiling of Testicular Germ Cell Tumors Reveals High Expression of PD-L1 and PD-1

Penis/Testis/Urethra: Benign Disease & Malignant Disease I session at the AUA 2016 describes the Immune Profiling of Testicular Germ Cell Tumors and Revealed High Expression of PD-L1 and PD-1. Activation of the immunosuppressive PD-1/PD-L1 (programmed death ligand 1) pathway has been shown to be an important immune surveillance evasion mechanism in solid tumors.

Testicular germ cell tumors (TGCT) have been long recognized to harbor extensive lymphocytic infiltrates, suggesting a dominant role for immune editing in these lesions. The authors evaluated the tumor specific immune microenvironment in TGCTs to determine a potential utility for immune checkpoint blockade therapies in these tumors. The authors profiled the immune infiltrate in TGCT with particular focus on immune checkpoint and T-regulatory cell function. Using validated immunohistochemical stains for PD1 (anti-PD1 antibody "ab52587"), PDL-1 (Cell Signaling, E1L3N, 1:100), FOXP3 (eBioscience, 236A/E7, 1:250) and a double immunostain for CD8 and ki67 (Thermo Scientific, SP16, 1:900 and Invitrogen/Zymed 7B11, 1:900; respectively), applied to TMA sections, they evaluated a retrospectively collected cohort (1995-2008) of 98 TGCT that comprised of 47 seminoma, 14 teratoma, 1 chorioncarcinoma, 13 yolk-sac tumors and 23 embryonal carcinoma. The authors found immunoreactivity for PD-1 and PD-L1 in 96/98 (94%) and 69/98 (70%) respectively.

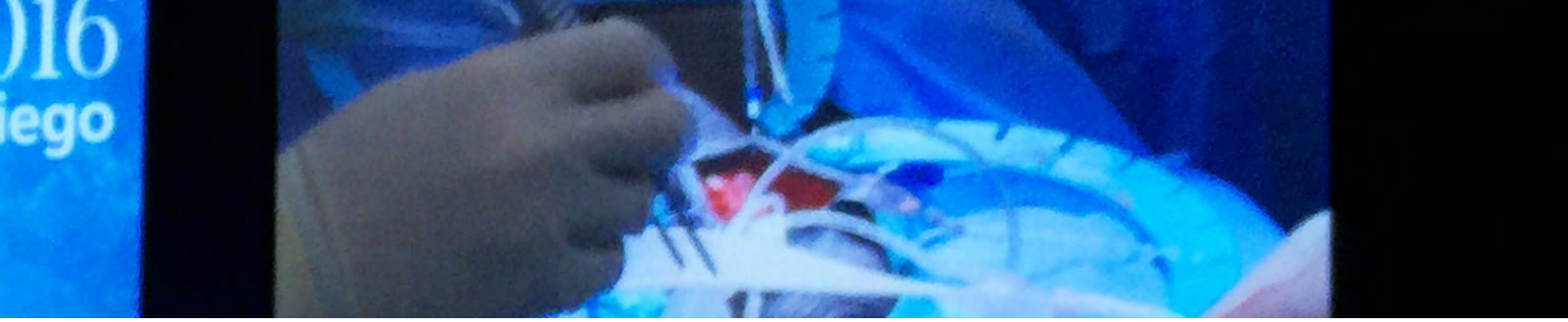
Notably, PD-L1 expression was predominantly found in infiltrating immune cells and was detected in seminoma and embryonal GCT cells. Positivity for PD-1 correlated with the overall extents of immune infiltrate. FOXP3 positive cells were detected in 87/98 (88%) lesions and a positive correlation between the CD8 positive infiltrate and FOXP3 positive cells was observed.

The extent of proliferating cells T-cells (as determined by CD8 and ki67 double positive immunoreactivity) was associated with PD1 expression ($r = 0.41$).

The authors conclude that regulatory T-cell infiltrate and PD-1 and PD-L1 expression are common features in germ cell tumors. This may suggests that therapeutic approaches involving immune checkpoint molecule blockade might be beneficial in patients with TGCT.

PRESENTED BY: MICHAEL HAFFNER, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MIKI HAIFLER MD. FOX CHASE CANCER CENTER, PHILADELPHIA, PA



Survival outcomes of adolescent patients with non-seminoma testicular germ cell tumors: A population based study

Testicular germ cell tumors (TGCT) are the most common solid malignancy in adolescent and young adult men. In adolescents, approximately 90% of TGCTs are non-seminomas (NS). Very few data exists on the impact of age, specifically adolescence, on outcomes of NS TGCTs. The authors were interested in this specific cohort of young patients. They examined The SEER database for individuals ≥13yr diagnosed with NS TGCTs from 1995-2012. Patients were categorized into adolescent (13-19yr) and adult (≥ 20yr) cohorts. A Cox proportional hazards model was used for multivariate analysis (MVA). 13,964 patients (1,496 adolescents, 12,467 adults) were included. Median follow up ranged from 1-215 months. 5yr OS and CSS for adolescent and adult patients was 94% VS 92% and 95% VS 94% respectively. Multivariable analysis revealed improved OS (HR, 0.61; 95% CI, 0.50-0.75; p<0.001) and CSS (HR, 0.65; 95% CI, 0.51-0.82; p<0.001) in the adolescence group. In a logistic regression analysis adjusting for demographics, compared to adults, adolescent patients more commonly presented with regional or distant metastatic disease (OR 1.16; 95% CI, 1.01-1.35), were more likely to undergo an additional tumor excision (OR 2.43; 95% CI, 1.57-3.77) and other adjuvant surgery (OR 5.87; 95% CI 2.25-15.3). Additionally, adolescents were less likely to undergo radiation (OR 0.61; 95% CI, 0.39-0.97). The authors conclude that adolescent patients with NS TGCTs had slightly improved survival compared to adults, despite more advanced disease. This may imply that while adolescent patients present at more advanced stage, they achieve excellent survival outcomes but possibly at the cost of greater therapeutic burden. The main limitation of the study is lack of ability to analyze RFS.

PRESENTED BY: NICHOLAS COST, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MIKI HAIFLER MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA

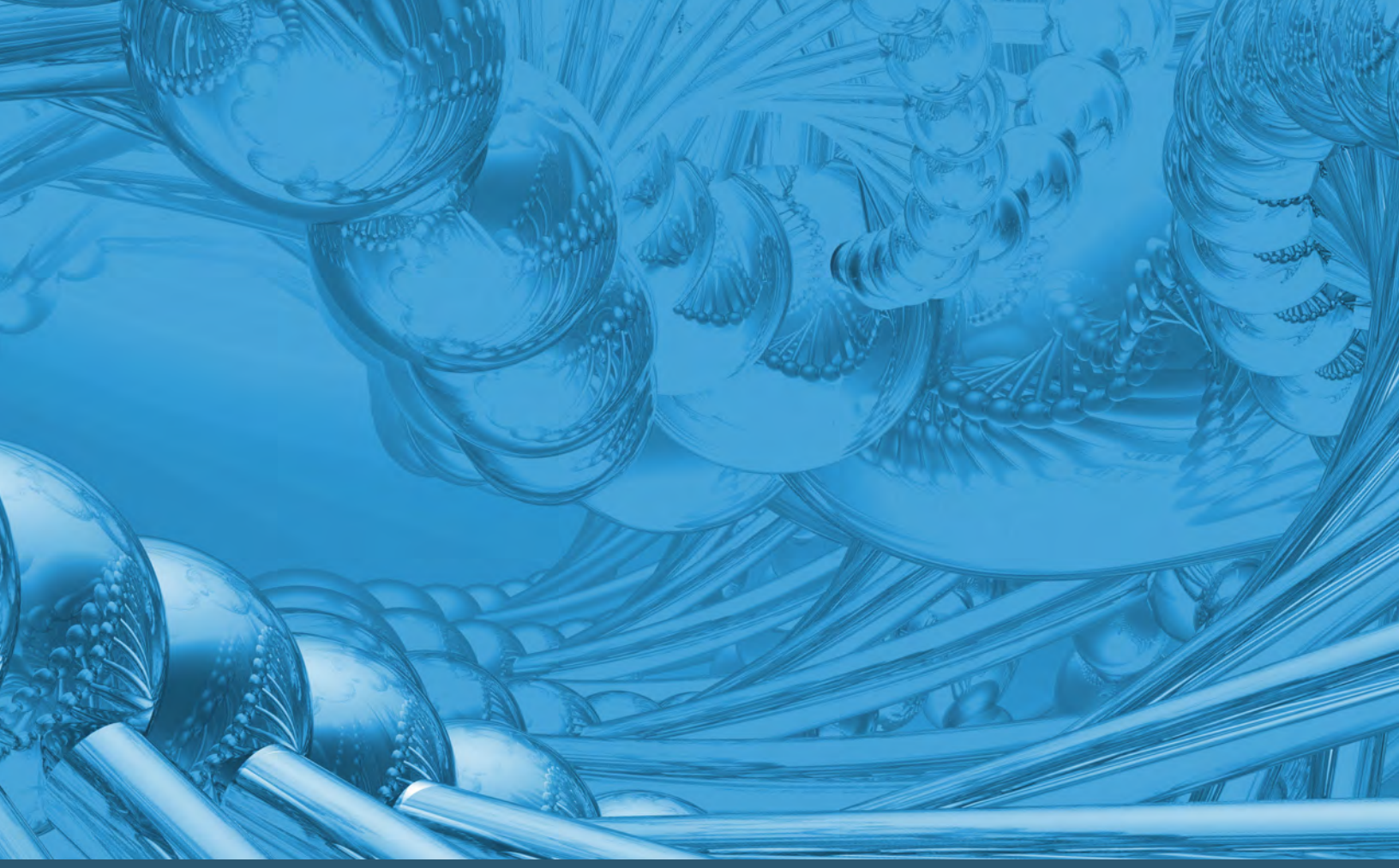
The Incidence and Treatment of Hypogonadism in Patients with Testicular Cancer

A very interesting podium presentation was presented at the AUA 2016 that described The Incidence and Treatment of Hypogonadism in Patients with Testicular Cancer.

Dr. Jamal Nabhani reminded all that even though the diagnosis of testicular cancer (TC) has been associated with hypogonadism, the mechanistic and clinical interrelation remains unclear. The authors investigated the pattern of diagnosis and treatment of hypogonadism in men with TC. They used Humana administrative claims data from 2007-2013 and identified men with and without a diagnosis of TC. Testosterone laboratory and prescription data were analyzed between the cohorts and by decade of life in order to adjust for differences in the rates of hypogonadism with age. 2,647 men with and 6.3 million without TC were identified. 428 men with testis cancer (16.2%) had a serum testosterone checked. 211 of the 428 men with TC who had a serum testosterone measured (8.0% of all men with testis cancer) were found to have a low serum testosterone. The OR of having a low testosterone was 3.8 in men with TC compared to controls. In terms of ART, 225 men (8.5%) with TC were prescribed testosterone. The OR of receiving a prescription was 4.5 95% CI [4.2,5.5] times higher than in men without TC and disproportionately high in younger men, with an 8.1 fold increase in the third decade of life. The authors conclude that Men with a diagnosis of TC are four times more likely to have a serum testosterone checked, be diagnosed with hypogonadism, and receive ART. Serum testosterone is measured and more frequently found to be low in elderly patients with a history of TC compared to age-matched controls. Additionally, hypogonadism predates the diagnosis of testis cancer in 2% of patients.

PRESENTED BY: JAMAL NABHANI, MD, AT THE 2016 AUA ANNUAL MEETING – MAY 6-10, 2016, SAN DIEGO, CA

WRITTEN BY: MIKI HAIFLER, MD; FOX CHASE CANCER CENTER, PHILADELPHIA, PA



We hope you enjoyed this issue of Everyday Urology™ – Oncology Insights™!

For your chance to win an Apple® iPad Pro™, please register at: OncToday.com/subscriptions OR UroToday.com/subscriptions

Registration allows for our readers to continue to receive the print publication, subscribe to emails based on your preferences and access to free, daily aggregated content in the areas of urology and oncology.

DIGITAL SCIENCE PRESS