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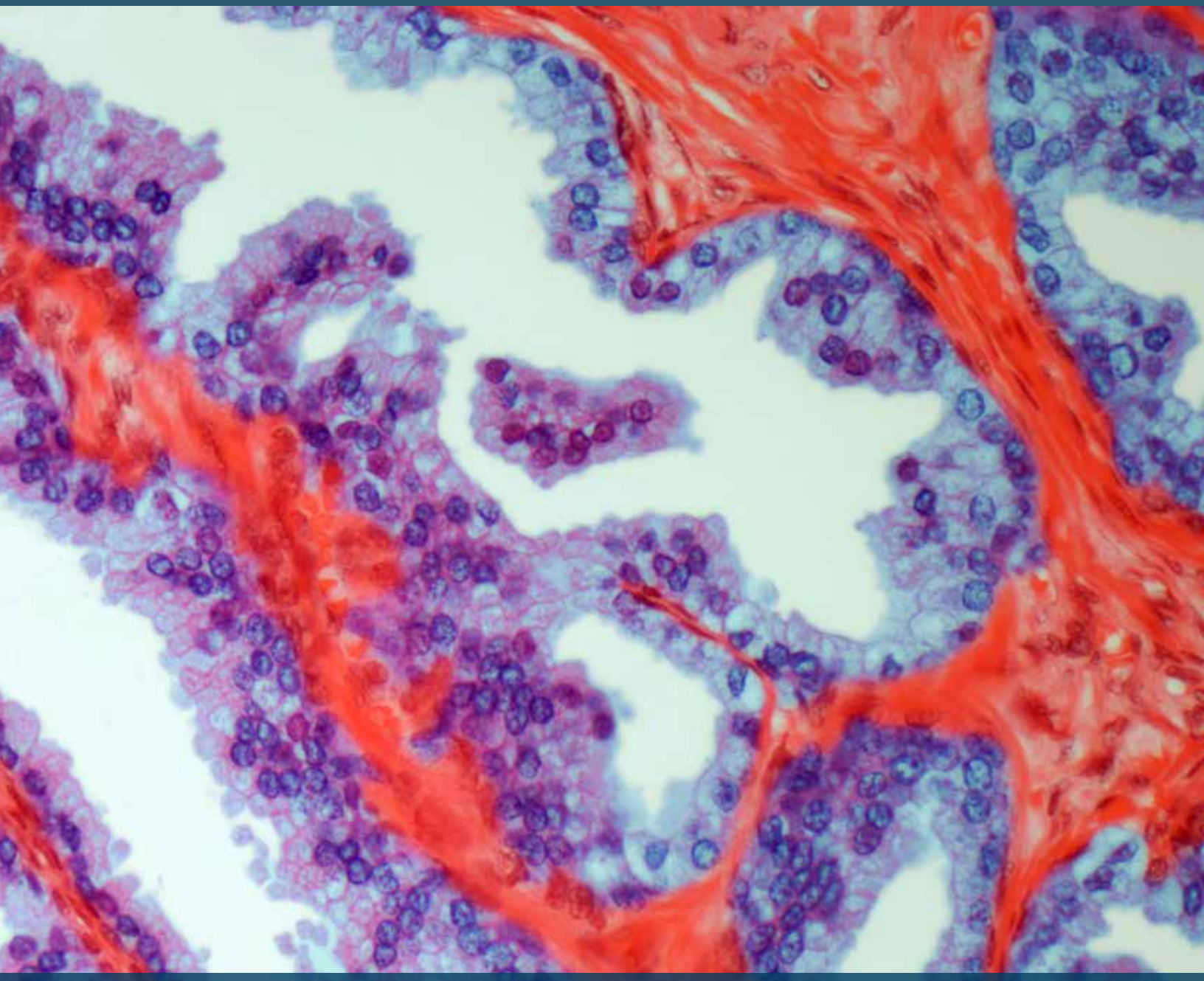

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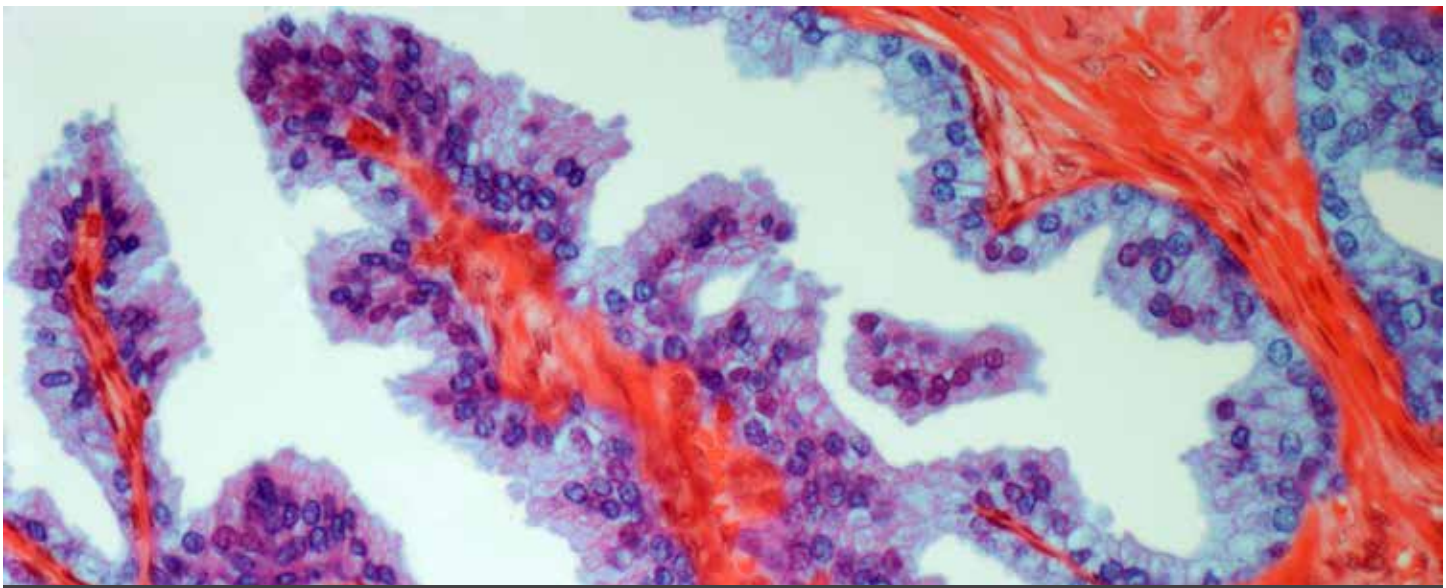

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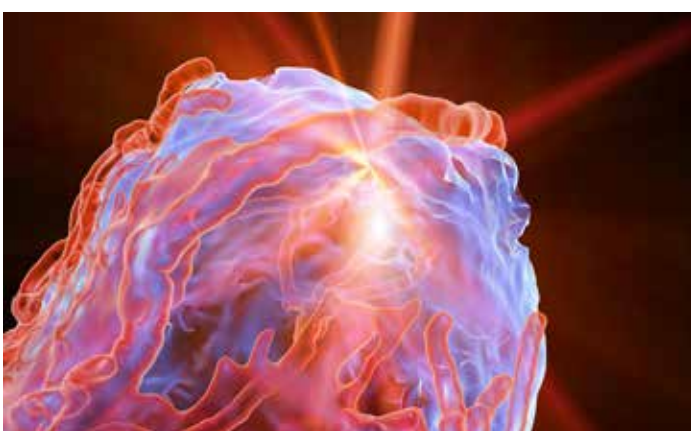

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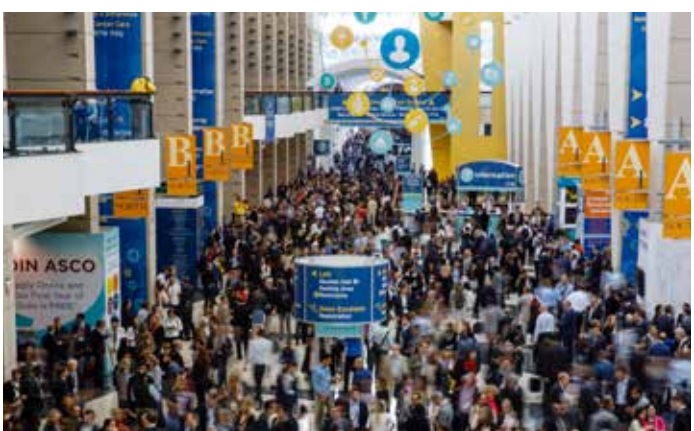

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FROM THE DESK OF THE EDITOR

Dear Colleagues:

Optimizing the patient clinical outcome (prolonging survival, preserving quality of life, and preventing complications) while avoiding excessive healthcare economic burden is tantamount to the overall improvement of the healthcare system. Certainly, combining an integrative, multidisciplinary approach, which can attain these aforementioned goals will align with the ''Triple Aim'', which proposes that improving the U.S. health care system requires simultaneous pursuit of three aims: improving the experience of care, improving the health of populations, and reducing per capita costs of health care.

Given the exceptional abundance of breakthrough diagnostics and therapeutics within all of oncology, and especially GU oncology, specialty as well as allied healthcare collaboration is essential for the treatment of GU cancer patients. At the University of Texas Medical Branch, Stephen Williams recently initiated a urologic oncology multidisciplinary care center (MDCC). In this issue's cover story, Dr. Williams and his former colleague, Ashish Kamat collaborate on their experiences and address the reasoning as well as the challenges of establishing a MDCC and review the implementation and factors impacting its success toward improving patient care. An MDCC can potentially benefit both academic and community based care, with disease focus that may be disease or specialty specific; hence, the need for the development of an Advanced Prostate Cancer Clinic(APC), an Advanced Bladder Cancer Clinic(ABC), an Advanced Kidney Cancer Clinic(AKC) is now in keeping with the well-known heterogeneity of GU cancers. We recognize the heterogeneity of our clinical practice environments, and thus if we can adopt the learnings and experiences from Dr.s Williams and Kamat and their MDCC, this should offer other practices and centers concepts and goals for improvement. LUGPA, SUO, and AUA are also continuing to offer courses that can assist busy clinicians with up to date developments and information within GU oncology but also frameworks for initiating and/or enhancing their MDCC or Advanced GU Oncology Clinic(APC, ABC,AKC).

This issue of *Everyday Urology* will review The Tenth Symposium on Targeted Alpha Therapy (TAT-10) which took place in Kanazawa, Japan. UroToday covered this program, recognizing that the field of targeted alpha therapies is evolving very rapidly, with Radium 223 heralding the 1st TAT to achieve therapeutic approval for mCRPC patients with bone metastases. The TAT-10 presentations reviewed the latest developments in radiotherapy with alpha emitters in multiple cancer types. This issue's Expert Perspective provides a summary of the findings from the meeting, discussing four of the major alpha emitters under active trial development; radium-223, thorium-227, actinium-225, and astatine-211. A top highlight of the meeting was Professor Joe O'Sullivan of Queen's University, Belfast, Ireland symposium which summarized bench to bedside for targeted alpha therapy and the ever evolving treatment for mCRPC.

Finally, at the 2017 Annual ASCO meeting there were two landmark phase III trials presented for patients with newly diagnosed metastatic prostate cancer, combing traditional androgen deprivation therapy (ADT) with abiraterone acetate/prednisone versus ADT, specifically, the LATITUDE trial, Fizazi et al and the STAMPEDE trial, James et al. The overall survival results of both trials were compellingly positive for the combination arm, thus now adding further important discussion and evaluation regarding specific newly diagnosed prostate cancer populations most appropriate for this combined approach vs chemohormonal therapy as well as the ongoing questions regarding sequencing, cost, and accessibility. These seminal studies, both published in New England Journal of Medicine, last month, and over 20 more selected conference commentaries are featured in our Spotlight section from both this year's annual ASCO and AUA meetings. For all of us dedicated to the care of advanced GU oncology patients, it is an invigorating and inspiring era, and this issue will hopefully allow you to enjoy some of these breakthrough developments.

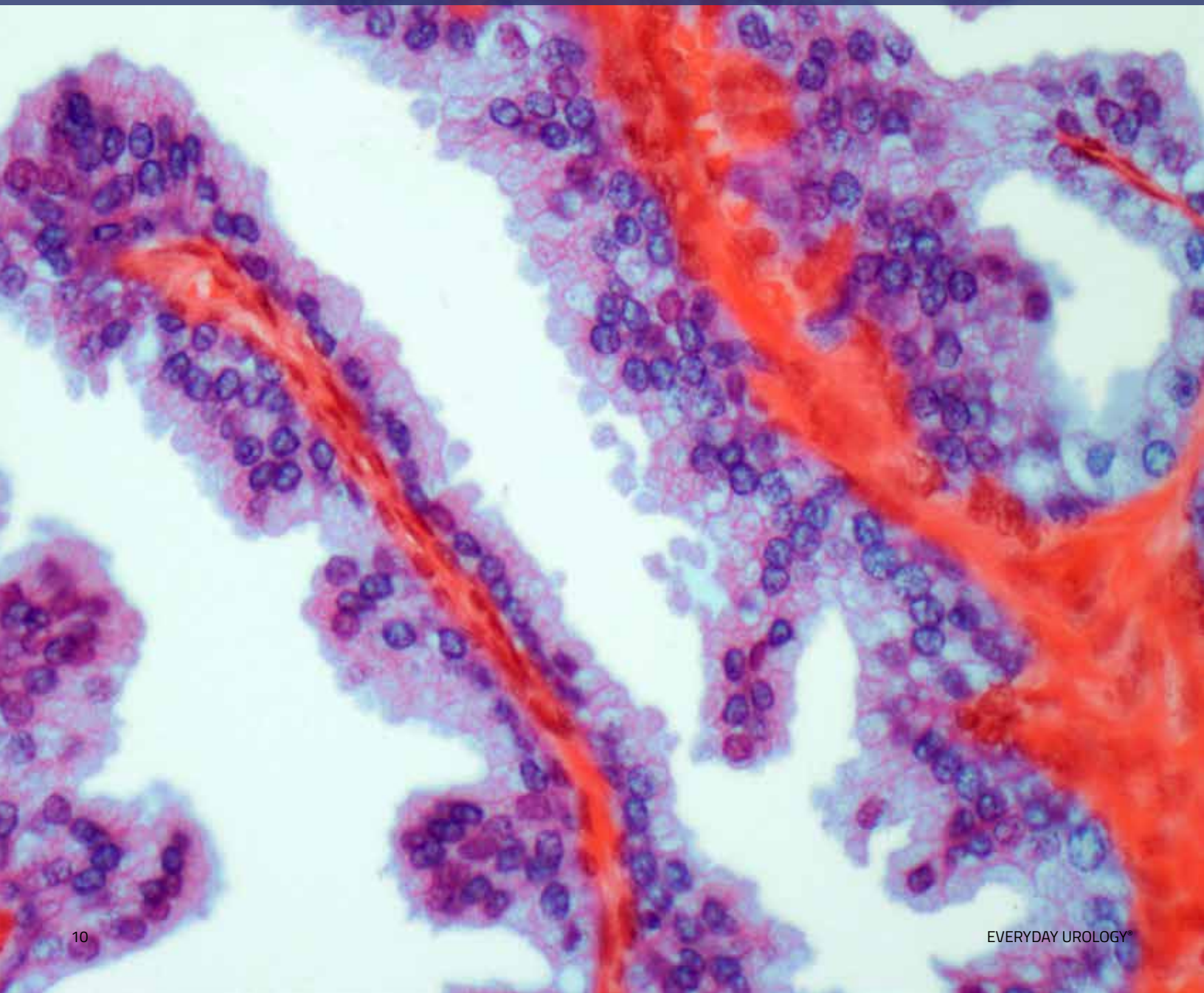
Thank you for your ongoing readership and feedback.

Sincerely,
NEAL SHORE, MD, FACS

Neal Shore, MD, FACS *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.*

The Multidisciplinary Approach to Prostate Cancer Management: From Diagnosis and Beyond

By Stephen B. Williams, MD and Ashish M. Kamat, MD, MBBS, FACS



DR. STEPHEN B. WILLIAMS is Assistant Professor, Tenure-Track in Urology, Robert Earl Cone Endowed Professorship, Director of Urologic Oncology, Director of Urologic Research and Co-Director for the Department of Surgery Clinical Outcomes Research Program at the University of Texas Medical Branch at Galveston. Dr. Williams completed Urology residency at Harvard Medical School's Brigham and Women's Hospital followed by a Society of Urologic Oncology fellowship at the University of Texas MD Anderson Cancer Center. He is the prior recipient of the American Urological Association (AUA) Gerald P. Murphy Scholar Award and his research has been awarded first prize for clinical research by the New England Section of the AUA and more recently Best Research Award at the 2016 annual AUA meeting. He is the author of over 100 peer-reviewed manuscripts and book chapters dedicated to urologic oncology and health services research.

ASHISH M. KAMAT, MD is a Professor (Tenure) of Urology and Director of Urologic Oncology Fellowship at M.D. Anderson Cancer Center, and a graduate of the AUA Leadership Program. Dr Kamat has authored over 200 publications, editorials & book chapters in prestigious journals; he is listed in 'Who's Who in Medicine' and 'Best Doctors in America' and has won the Compassionate Doctor Award from patient groups. He is an exceptional educator nominated twice for the Robert M. Chamberlain Distinguished Mentor Award and has been invited as a visiting professor to several universities across the world. Dr Kamat is Co President, International Bladder Cancer Network, Chair, Bladder Cancer Think Tank (2015), Chair, Bladder Cancer Task Force for SITC, actively participates in various global urologic efforts, and serves on the board of regional and national societies for Urology.

Prostate cancer is the most common cancer in American men. The American Cancer Society's estimates for prostate cancer in the United States for 2017 are 161,360 new cases of prostate cancer and 26,730 deaths from prostate cancer.[1] Approximately 11.6% of men will be diagnosed with prostate cancer at some point during their lifetime, based on 2012-2014 data.[2]

INTRODUCTION

When patients receive a diagnosis of cancer it can be devastating. Suddenly their world is turned upside down, populated by doctors, diagnostic tests, and treatments. The standard process for newly diagnosed patients with prostate cancer is a chronologically linear and often one-dimensional process managed by urologists.[3] If the patient's diagnosis is based on biopsy results, the urologist discusses treatment options with the patient and his family. This may be followed by referral to another specialist such as a medical and/or radiation oncologist depending on their risk stratification.[4] Sometimes patients immediately choose to have surgery without learning about radiation therapy options. Compounding the patients' anxiety about their cancer diagnosis is the burden of making a treatment decision and dealing with the complexities of the health care system. Some patients are uncomfortable with the responsibility of choosing a treatment and would prefer that the physician tell them what to do. Many patients have a sense of inadequacy to understand the terminology, treatment options, and associated long-term ramifications. Recommendations to meet with the nurse educator for educational counseling and support are not consistently offered to patients. Difficulties getting immediate appointments further contribute to the anxiety in decision making. Patients from out-of-state, and particularly out-of-country, often experience additional anxiety managing this process long distance.[5,6]

Physicians may also feel challenged to meet the demands to stay current with the rapidly changing science and expanding number of treatment options as research has allowed more treatment modalities to move from the research laboratory to the clinical setting. Increasing specialization has led many cancer treating physicians to limit their practice to specific cancer types. This is a benefit care for specific patient problems, but may lead to narrow-minded tendencies. Thus there is a growing need to

Compounding the patients' anxiety about their cancer diagnosis is the burden of making a treatment decision and dealing with the complexities of the health care system.

coordinate care among providers, ensuring that patients successfully negotiate the complexities of cancer care.[3,7]

MULTIDISCIPLINARY APPROACH FOR CANCER CARE

As early as the 1990s it was becoming clear that multidisciplinary care clinics provide an effective way to deploy expertise while simultaneously being more cost efficient.[8] Theoretically, a multidisciplinary approach provides a rational and coordinated way to evaluate and treat patients with complex diseases by bringing health care providers in the surgical, medical, and radiation oncology disciplines together. In reality, each discipline functions in a different environment with different requirements and incentives that can undermine seamless coordination. For the most part the practice of medicine relies on consulting different specialty services concerning individual patient problems, however there has been a growing movement towards integrating multiple specialties into a multidisciplinary care center (MDCC). The MDCC has been playing an increasingly prominent role in cancer care, both in the community and in academic cancer centers. It is becoming more common in the practice of many oncological disciplines including prostate cancer.[8,9,10,11,12]

For patients diagnosed with cancer, coordinated disease management among physicians in different specialties at a single location makes multidisciplinary care clinics an indispensable resource.

MULTI-DISCIPLINARY CLINICS IN NON-UROLOGICAL CANCERS

A cancer center tends to be organized into distinct disease centers. Each center may have its own disease-based multidisciplinary clinic, the needs of which differ from another center. This is particularly true in large academic centers where specialized providers treat patients with a single disease.[13]

Multidisciplinary clinics play a prominent role in many cancer centers but their structures differ by institution. When two different structures were compared, one in which patients are seen sequentially by physicians from each discipline, and a second in which patients are seen concurrently by physicians from each discipline, more than 90% of providers enjoyed working in an MDCC and more than 75% preferred to see new patients in an MDCC. Additionally, 90% believed that patients perceived the clinics to be valuable for comprehensive, coordinated, and appropriate care. However, satisfaction differed between patients and physicians. One third of the physicians thought the clinics were not an efficient use of their time, whereas patients seen in each clinic model uniformly expressed high satisfaction with the coordination of care.[13]

For patients diagnosed with cancer, coordinated disease management among physicians in different specialties at a single location makes multidisciplinary care clinics an indispensable resource. They provide patients the opportunity to receive individualized treatment plans in the broad context of multiple specialists all within a single encounter. MDCC models are important decision-making forums in current oncology practice.[9] An MDCC forum can foster physician coordination to generate comprehensive patient care plans, but it may also have medicolegal implications.[10]

Measurements of success are principally by patient and physician satisfaction surveys, and downstream revenue, calculated by determining revenue generated by surgery, pathology, clinical laboratory, imaging, chemotherapy, radiation therapy, and in-patient services.[3] Although an MDCC is purported to offer benefits to patients, there is little evidence about the benefit to individuals receiving care at community cancer centers in the United States. Among community cancer centers serving patients diagnosed with colon, rectal, or lung cancer the relationship between the level of implementation of an MDCC and various processes of cancer care such as time to treatment receipt or evaluation for enrollment onto a clinical trial is notably limited.[9]

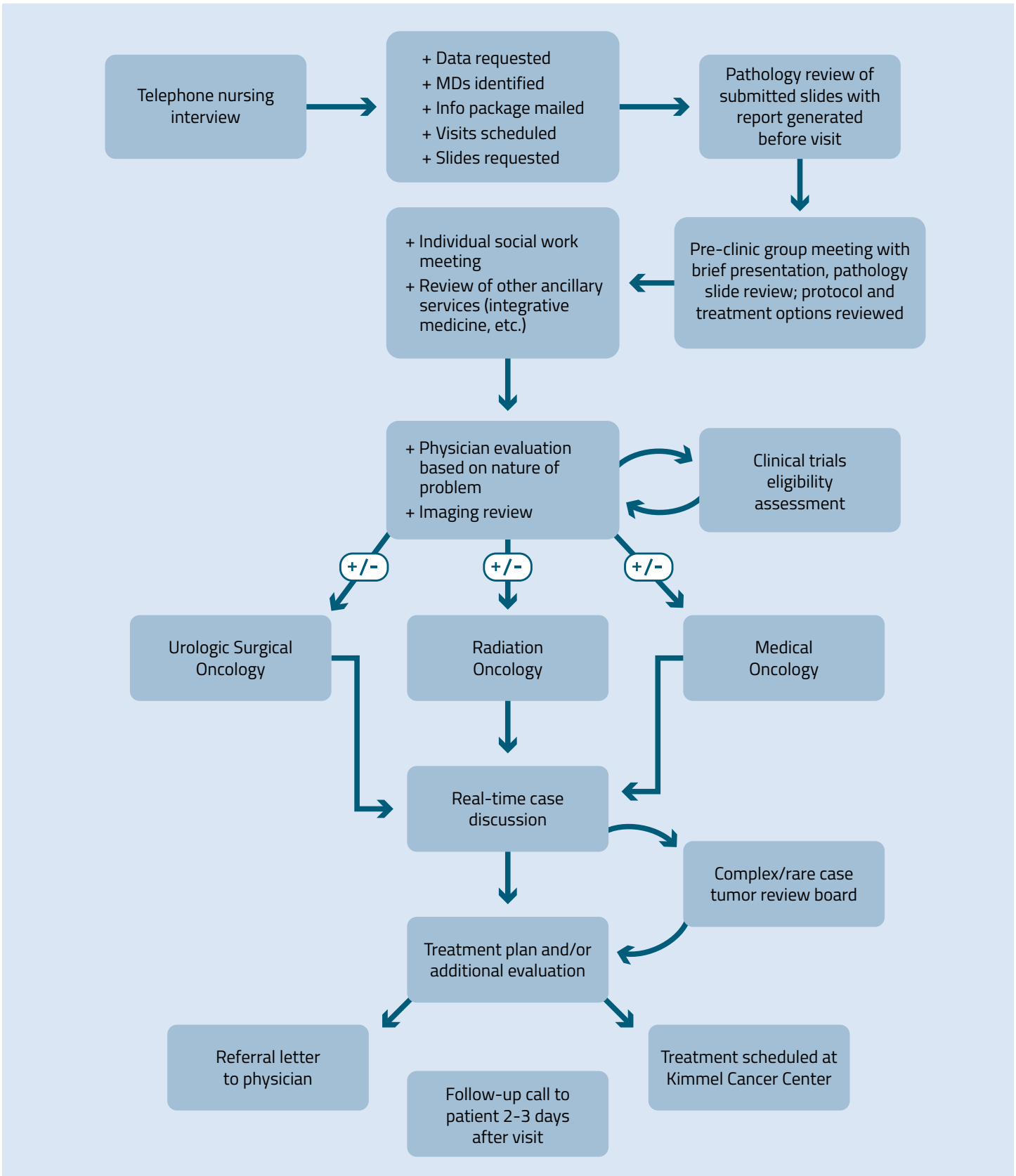
The rigorous study of the use of multidisciplinary cancer care is scant despite the overall observations of its use. One such objective study showed the benefit of an MDCC to improve the use of standardization and adherence to evidence based medicine to provide better care was demonstrated in an Australian study of 335 patients with non-small-cell lung cancer.[11]

Gradually multidisciplinary care clinics have been shown to improve cancer specific survival in brain, breast, lung, colorectal, and head and neck.[7,14,15,16,17] An increase in the number of patients screened for and enrolled in clinical trials has also been demonstrated after implementation of a MDCC in a gynecologic oncology center.[15] Improved patient access to consultations and shorter time to initial treatment was observed in a study of MDCC in pancreatic cancer following the establishment of a multidisciplinary pancreas tumor clinic.[14] This same report also cited that one group has reported that after establishing a multidisciplinary pancreatic cancer clinic, 23.6% of their patients had a change in their recommended management and 77.8% of patients enrolled in the National Familial Pancreas Tumor Registry.[18] After three decades MDCs are able to show not only improved patient and provider satisfaction, but improved patient access to care.[14]

MULTI-DISCIPLINARY CLINICS IN UROLOGICAL CANCERS

Our literature review of MDCCs for urological cancer revealed remarkably few. We found no studies specifically for testicular cancer or renal cancer and only one related publication specifically for bladder cancer.[19] One prospective study of a multidisciplinary approach to urological malignancies reported

Figure 1: Patient flow through the multidisciplinary genitourinary cancer clinic based on the current model.



38% of newly diagnosed patients had a change in diagnosis or treatment. Changes in treatment were most common in bladder cancer (44%), followed by kidney (36%), testicular (29%), then prostate (22%) cancers.[20]

MULTI-DISCIPLINARY CLINICS IN PROSTATE CANCERS

Publications for prostate cancer are the most extensive, nevertheless they too are limited. One Canadian study reported on a large, in depth assessment of their diagnostic assessment program for newly diagnosed prostate cancer within an MDCC.[21] In this report, more than 80% of patients had timely multidisciplinary consultation which was associated with different management decisions.

A few years ago an Italian study reported on management changes following 6 years after the establishment of multidisciplinary prostate cancer clinic.[6] Not unexpectedly, results showed that patients with prostate cancer should be comprehensively informed about the disease, the therapeutic and observational strategies available, the therapy-induced adverse effects, and the rehabilitation programs, and should be accompanied in the decision-making process. They should be able to understand the pros and cons of their options, the therapy-induced adverse effects, and the available rehabilitation programs, thus becoming active participants in the decision-making process. Realistically, this is frequently not the scenario. The report delivered a rap on the wrist with the finding to consumers and to the marketing industry. Sophisticated technologies and therapies and the amount of information available in the press and on the internet, combined with the consumer's demand for the 'best treatment' available and their inability to distinguish between evidence-based medicine and marketing strategies.[22]

Patients with prostate cancer should be comprehensively informed about the disease, the therapeutic and observational strategies available, the therapy-induced adverse effects, and the rehabilitation programs, and should be accompanied in the decision-making process.

Although the multidisciplinary setting is often viewed as an ''inefficient'' use of time in terms of the numbers of patients that can be seen by an individual clinician, a retrospective study demonstrated potential outcome benefit to many patients. This study at Duke University Medical Center compared a prostate cancer multidisciplinary clinic against their standard urology clinic model. Neither a difference in outcomes over a 4-year period, despite higher risk disease in the MDC population, nor any delay in time to radical prostatectomy was found.[23] On the other hand, a report of an evaluation of 15 years of data from a prostate cancer MDCC reported a 10 year survival data for stage 3 and 4 prostate cancer had an institutional survival rate that exceeded the government SEER (Surveillance, Epidemiology and End Results) data together with high patient satisfaction. This study also underscored the importance of interdisciplinary educational aspects and patient satisfaction.[7]

The options for the management of localized prostate cancer include active surveillance, surgery, radiotherapy, cryotherapy, or other investigational methods and each option has many subsets. Patients and physicians need to be informed of the risks and benefits of each option.[24] The impact of multi-disciplinary meetings was the subject of a systematic review of the literature. The reviewers found that patients discussed at meetings were more likely to receive more accurate and complete pre-operative staging, and neo-adjuvant/adjuvant treatment. In prospective studies, between 4% and 35% of patients discussed had changes in assessment and diagnosis following the meeting.[25] Of the only two urological oncology studies reviewed, one study[26] found no changes in management, whereas the second study[27] found changes to the original treatment plan in 26.7% of all urological cases (66.7% for testicular cancer, 42% for bladder cancers, 26% for prostate cancers, and 19% for kidney cancers). High impact cases, those with either a major change in the management plan, or a plan developed where there was none, were twice as likely in patients with metastatic disease.

IMPLEMENTATION OF A MDCC: THE UNIVERSITY OF TEXAS MEDICAL BRANCH EXPERIENCE

To the author's knowledge no study has addressed the implementation of a prostate cancer MDCC with respect to disease risk, time to survival, and quality of life. We at the University of Texas Medical Branch (UTMB) recently instituted a urologic oncology multidisciplinary center to address the issues of an MDCC and to evaluate the structure and operation of the clinic to highlight factors impacting success in improving patient care and outcomes of patient care. A formal evaluation of UTMB's urologic oncology center to measure outcomes and quality data will be used to determine areas of improvement.

The need for the long-term commitments of all participants and the institution cannot be underestimated in establishing a multidisciplinary clinic. In our plan all newly diagnosed prostate cancer patients must be evaluated in the MDCC. The patient is enrolled in the Prostate Cancer Registry and the case is then presented to the tumor board. The patient's referring urologist is given the findings of the case and the board's recommendations. The patient is always involved in their care and has the final say in deciding on the treatment.

Effective patient care in a multidisciplinary setting needs a team champion, and the involvement of the physicians on the team for a concerted and coordinated activities of multiple disciplines. When this occurs there is a perception of greater team effectiveness. Contributing to a perception of team effectiveness is patient education, patient satisfaction, balance among

culture values, openness to innovation, and adherence to rules and accountability. Perceived team effectiveness, in turn, was consistently associated with both a greater number and depth of changes made to improve chronic illness.[12]

In 2011 a reporting and quality improvement system was developed by the Commission on Cancer (CoC) of the American College of Surgeons to assist CoC-accredited cancer programs in promoting evidenced-based cancer care at the local level. The Rapid Quality Reporting System (RQRS) is a Web-based, systematic data collection and reporting system. Beginning January 2017, RQRS participation will be required for all CoC-accredited programs. The RQRS advances evidenced-base treatment through a prospective alert system for anticipated care which supports care coordination required for breast and colorectal cancer patients at participating cancer programs. The System provides real clinical time assessment of hospital level adherence to quality of cancer care measures. It is well studied in breast and colorectal cancer[9,28] but so far not in urological cancers.

We anticipate that the treatment in the environment of the new multidisciplinary clinic will demonstrate with improved processes of care, evidenced by: (1) shorter time to initial therapy receipt, (2) increased likelihood of multi-modality therapy receipt, (3) increased likelihood of clinical trial enrollment evaluation, and (4) increased likelihood of adherence to National Comprehensive Cancer Network (NCCN) treatment guidelines, (5) patient satisfaction, (6) and lower costs.

CONCLUSIONS

The literature shows many benefits of an MDCC including patient satisfaction, increased accuracy of care, decreased time to follow-up and treatment, better quality of life, enhanced graduate medical education, better adherence to national cancer guidelines, and improved survival in multiple non-urological cancers. These benefits were largely studied in non-urological cancers. The literature for an MDCC in urological cancers is sparse and the majority of the literature found was for prostate cancer. This represents an area of need, especially in the context of testicular, bladder, and renal cancer. The RQRS system has yet to be evaluated in the context of urological cancers despite being a mandated requirement

We look forward to further study. Some potential future projects would include: prospective survey of patient perceptions of the urological MDCC; comparison of our patient population pre/post MDCC of follow-up time, time to treatment, increased NCCN guideline adherence, increased clinical trial enrollment, decreased duplicated tests, decreased time to treatment; evaluate plan changes following multi-disciplinary tumor board meetings.

In this era of value-added medical practice, cost benefits can be evaluated analysis of various metrics, such as reduced costs by omitting duplicated tests. Possibly downstream revenue would be generated by an MDCC. ■

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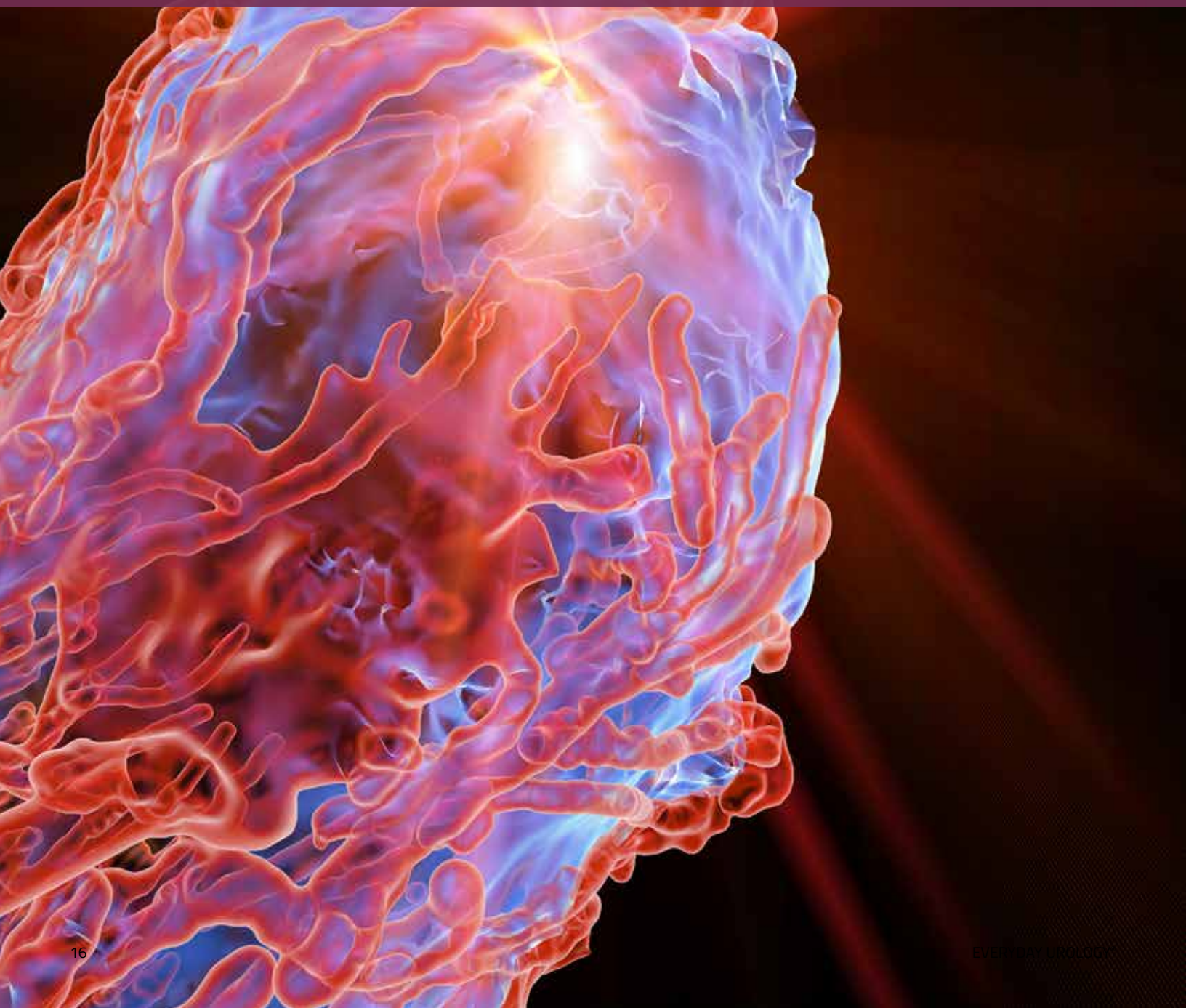
A REVIEW ON THE DEVELOPMENT OF TARGETED ALPHA THERAPY IN THE TREATMENT OF CANCER:

Focusing on The First and Only FDA Approved Targeted Alpha Therapy Radium-223 in the Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

By William C. Carithers, Jr., PhD



WILLIAM C. CARITHERS, JR., received his BS degree in Physics from the Massachusetts Institute of Technology in 1964. He went on to earn his PhD degree in Physics from Yale University in 1968. Dr. Carithers was a Sloan Fellow from 1972 to 1974. After faculty appointments at Columbia University and the University of Rochester, he moved to Lawrence Berkeley National Laboratory in 1975 where he worked until his retirement in 2014. He has conducted research in high-energy physics at Brookhaven National Lab, Stanford Linear Accelerator Center and Fermi National Accelerator Lab (Fermilab). As the spokesperson for CDF, the Collider Detector at Fermilab collaboration, he co-led the team that discovered the top quark. He turned his research effort to cosmology, working on two techniques to measure the expansion history of the universe. Following his retirement, he developed an interest in the research of targeted alpha particle therapy for cancer treatment.

INTRODUCTION

The Tenth Symposium on Targeted Alpha Therapy (TAT-10) opened on Wednesday, May 31, 2017 in Kanazawa Japan. The symposium was jointly organized by the Joint Research Centre (JRC) of the European Commission and Kanazawa University as a forum for presentations on the latest developments in radiotherapy with alpha emitters in cancer. With over 200 participants the symposium covered advances in cancer treatment using alpha emitters as targeted therapy, clinical and preclinical research, radionuclide production, instrumentation and dosimetry.[1]

Four of the major alpha emitters radium-223, thorium-227, actinium-225, and astatine-211 will be discussed in this review that were presented during the TAT-10 Symposium. A significant milestone occurred for targeted alpha therapy when in 2013 radium-223 dichloride (radium-223) was approved by the FDA as the first in class and to date only targeted alpha therapy marketed as Xofigo®).[2,3] The approval of radium-223 was a major step forward in the treatment of metastatic castration resistant prostate cancer (mCRPC). The pivotal phase III ALSYMPCA (Alpharadin in the Treatment of Patients With Symptomatic Bone Metastases in Castration-Resistant Prostate Cancer) trial demonstrated statistically significant improvement in overall survival in patients with osseous metastasis.[4]

CLINICAL UPDATE

Treating men with advanced prostate cancer involves consideration of how to treat each patient, when to treat and what treatment or combination of treatments to use and importantly what tests to use to assess the benefits of the selected treatment. In a retrospective study of heavily pre-treated population with a 64% one-year survival, patients with mCRPC had improved survival if they received radium-223 before being treated with cytotoxic chemotherapy when they had elevated baseline serum alkaline phosphatase (ALP). What emerges from this and other prospective studies is the importance of using radium-223 earlier in the patient's disease when patients are more likely to receive the six planned cycles.[5]

Following the ALSYMPCA trial the patients were enrolled in an international, early access program (iEAP), open-label, single-arm phase 3b trial.[6] The purpose was to see if there were significant differences in asymptomatic patients at baseline compared to symptomatic patients for early treatment with radium-223. Asymptomatic was defined as no pain and no opioid use. Patients were excluded if they had malignant lymphadenopathy > 6 cm and visceral disease.[6]

Asymptomatic patients had received fewer prior treatments of abiraterone, enzalutamide, and docetaxel, and were more likely to complete the full treatment of 6 cycles of radium-223. Adverse events were less common in asymptomatic patients. Asymptomatic patients were more likely to show alkaline phosphatase (ALP) normalization (59% vs 34%).[7] Looking for candidates assessing efficacy for radium-223, an exploratory analysis of iEAP data revealed that ALP was a candidate for a biomarker of disease status. Median overall survival was longer in asymptomatic patients (median 20.5 months vs 13.5 months for symptomatic). Median overall survival was also longer in patients who received radium-223 plus abiraterone, enzalutamide, or both than in those who did not receive these agents. Similarly overall survival was longer in patients who received radium-223 plus docetaxel than in patients who received radium-223 without docetaxel.[7,8]

The investigators concluded that radium-223 can be safely combined with abiraterone or enzalutamide.[6] A decline in alkaline phosphatase was associated with longer overall survival, and time to first symptomatic skeletal events (SSE).[7] Patients who were asymptomatic, no pain and no opioid use at baseline, were more likely to have a better prognosis and to complete all 6 cycles of radium-223.[8]

Consequently, the treatment paradigm is shifting from what was the standard of care[9] to therapeutic layering[10] in mCRPC with immunotherapy – targeted alpha radium therapy – chemotherapy on top of continuing second generation androgen pathway inhibitors, traditional androgen-deprivation therapy, and best supportive care when further treatments will not improve survival.[6] Timing of delivering each treatment is critical. Treating early, before symptoms of pain develop from metastatic disease and monitoring markers of disease progression, then layering therapies is demonstrated to improve overall survival and quality of life.

BACKGROUND TO RADIATION

The use of radiation in medicine has a long history starting in the late nineteenth century with the notable discovery of radium by Marie Curie. The major types of ionizing radiation emitted during radioactive decay are alpha particles, beta particles and gamma rays [Figure 1].[11,12,13]

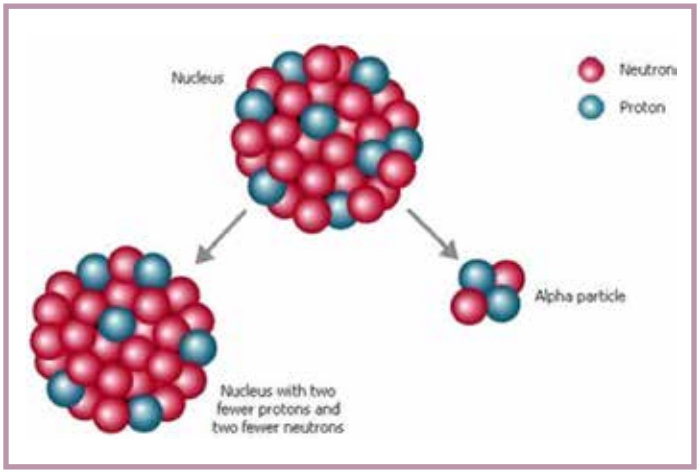


Figure 1: Alpha Particle Decay[10]

An alpha particle consists of two protons and two neutrons, the equivalent of a helium nucleus. Alpha particles are emitted from the decay of certain heavy radioactive nuclei, such as uranium, actinium and radium. They are very energetic and highly ionizing, i.e. short range (0.1 mm); high energy loss (50 - 230 keV/micrometer). The much high linear energy transfer (LET) causes irreparable damage to the cell DNA while the short range of the alpha confines the damage to the tumor thus reducing the damage to nearby healthy cells. External bodily exposure carries little risk to health, however, if inhaled or ingested, alpha particles can cause severe damage at both cellular and genetic level. This makes alpha particles possibly the most damaging form of radiation.[11,12, 13]

Beta-emitters have a relatively long radiation range and significant bone marrow exposure is associated with their use which has restricted bone treatment to pain palliation.[14] Beta particles are electrons (or positrons) emitted from certain nuclei during radioactive decay. They have longer range (110 millimeters) and lower linear energy transfer (0.2keV/micrometer) than alpha particles. To cause irreversible DNA damage and induce cell death beta particles require 102–103 tracks across a section of DNA, whereas alpha-particles require only 2–3 tracks. Common beta emitters include carbon-14 and strontium-90.[11, 12]

Terminology may be confusing. Measurements of radiation dose are given in Curies and/or Bequerels. Curie (Ci) is the traditional measure of radioactivity based on the observed decay rate of 1 gram of radium. One curie of radioactive material will have 37 billion disintegrations in 1 second. It has been replaced by the term Becquerel (Bq), the amount of a radioactive material that will undergo one decay (disintegration) per second.[13,15]

Some of the commonly used terms to quantify radiation are radioactivity, exposure, effective dose, and absorbed dose. Radioactivity is the amount of ionizing radiation released by a material. Exposure measures the amount of radioactivity travelling through the air. Absorbed dose describes the amount of radiation absorbed by an object or person. The most common unit of measure for this is the Gray (Gy), where one Gray is equivalent to one Joule per kilogram in the international system (SI) unit of radiation dose. The Gray (Gy) has replaced the term rad, and one Gray equals 100 rad. Effective dose combines the absorbed dose and the medical effects of the type of radiation. For beta and gamma radiation the Effective Dose (expressed in Sievert (Sv) is equivalent to the absorbed dose. For alpha radiation which is more damaging to the body, the Effective Dose may be greater.[11]

When reading "Dosage and Administration" of the Package Insert for radium-223, the instructions are in both the newer and the older terms. The recommended dose of radium-223 is 55 kBq (1.49 microcurie) per kg body weight, given at 4 week intervals for 6 injections.[3]

UNIQUE PROPERTIES OF RADIUM-223

Radium-223 is a bone-targeting radiopharmaceutical and can substitute for calcium during bone formation. It belongs to the same group in the Periodic Table of the Elements as alkaline earth elements (calcium (Ca), strontium (Sr), barium (Ba), and radium (Ra)) and has similar bone seeking properties.

Radium-223 is easily administered directly into the bloodstream.[3] It is a calcium mimetic and as long as the target is calcium, radium-223 is its own vector. This characteristic puts radium-223 in a special category. [14] It homes to bone and bone metastases where it can do its nefarious work in the tumors. It delivers an intense and highly localized radiation dose (with a range of 2 to 10 cell diameters) to bone surfaces. The higher LET of alpha-particles leads to a higher fraction of double strand breaks than with either beta-particles and gamma irradiation and leads to greater biological effectiveness. The cell is less able to repair DNA double strand breaks than single strand breaks. The number of DNA hits needed to kill a cell with an alpha particle is fewer than with beta emitters.[14, 16,17] Moreover, radium-223 does not require cells to cycle in order to achieve its antitumor effect. This is advantageous in the treatment of prostate cancer, which has a low proliferative rate.[18]

Radium-223 decays to daughters, spontaneously breaking down to release energy and matter from its nucleus. Together with its daughters (three of which are also alpha emitters) radium-223 is even more potent, causing double-stranded DNA breaks leading to cell death.[19] These characteristics represent hope for patients with CRPC and bone metastases. Targeted alpha therapy has the potential to inhibit the growth of micrometastases by selectively killing bone-derived cancer cells.

OTHER ALPHA EMITTERS FOR THERAPY

Several alpha-particle emitters with suitable half-lives are currently in use or being investigated for use in human trials: astatine-211 (211At, 7.2 h), bismuth-212 (212Bi, 1 h), bismuth-213 (213Bi, 45.6 min), radium-223 (223Ra, 11.4 d), actinium-225 (225Ac, 10.0 d) and thorium-227 (227Th, 18.7 d).

Different from radium-223 which homes to bone naturally, other alpha-emitting elements require a molecular vector to attach to the tumor of interest and to carry the alpha-emitting radionuclide. Generally the form for delivery to a tumor cell

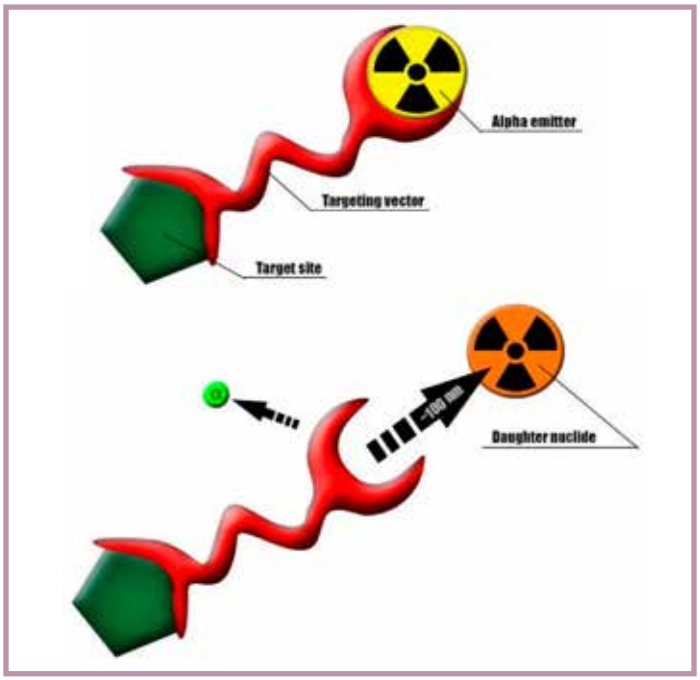


Figure 2: This illustration characterizes the targeting vector and a schematic representation of a recoiling daughter radionuclide detaching from a targeting agent as a consequence of alpha decay.[19]

consist of an antibody to a tumor surface antigen, attached to chelator and then to the alpha emitter. The alpha particle delivering structure is similar to a ''sandwich'' consisting of an antibody that attaches directly to an antigen in the tumor or on its surface, a chelating agent which acts as a linker to join the antibody to the radioisotope. Alpha emitters constructed for delivery can attack various tumor types in many locations, weeding out micrometastases. The vector combines the sciences of biology, chemistry and physics.[26]

Innovations galore were presented describing potential choices of the three components depending on the tumor of interest. The parameters that drive the choices include pharmacokinetics of the vector, the availability and half-life of the radioisotope, and the specificity of the vector to prevent accumulation in non-targeted organs.

There is a complication to this vector-targeting scheme. When the first alpha-emitting decay occurs, the recoil of the daughter nucleus is sometimes sufficient to break the molecular bond holding the radionuclide and the daughters are no longer bound to the tumor site [Figure 2]. Long-lived daughters can move through the body removing subsequent alphas from the tumor site and possibly damaging healthy organs, especially the liver and kidneys.[3, 20]

TO TAME THE DAUGHTERS

The main objective of targeted radionuclide therapy is the ability to selectively deliver cytotoxic radiation to cancer cells that causes minimal toxicity to surrounding healthy tissues. Utilization of appropriate carriers capable of retaining both the parent and the daughter products for the effective delivery of the radionuclide to the tumor site, while mitigating global in vivo radiotoxicity is an active area of research. The use of nanoparticles for this purpose was very much in evidence at the meeting. One potentially effective carrier of radium isotopes is a lanthanum phosphate core surrounded by nanoparticles to hold the radionuclide and retain the parents and daughters. 20 Investigation of this construct[22] and other nanoparticles as carriers such as gold[23], polymersomes[24] and others[25] were presented.

One innovative choice for the antibody part of the vector is the nanobody, the smallest, antigen-binding fragment from naturally occurring heavy-chain only antibodies. Nanobodies possess various advantages over monoclonal antibodies. The molecular weight of nanobodies (15 kDa) is one-tenth of that of conventional antibodies (150 kDa). Therefore, they have a lower immunogenicity due to their rapid blood clearance and high sequence identity to human variable domains of the heavy chain. Nanobodies are easy to produce and have high stability in harsh conditions, as well high affinity and specificity for their cognate antigen.[27] Several have been evaluated in pre-clinical studies.[28,29]

THE SHORT-LIVED ALPHA-EMITTERS, 211AT AND 213BI

The short-lived alpha-emitters, 211-astatine and 213-bismuth, may have potential as radioimmunotherapeutics in humans. Bismuth-213 has the disadvantage of a very short, 46 minute, half-life which usually requires direct injection into the tumor site.

Astatine-211 is an alpha-emitting halogen and has an acceptable half-life for cancer therapy (half-life =7.2 h). However, many astatine compounds that have been synthesized are unstable in vivo, providing motivation for seeking other astatine-211 labeling strategies. Most of the currently labelling protocols are developed based on iodine chemistry and lead to the formation of astatobenzoate-labelled compounds. Such labelling is unstable, contrary to the iodine case, when the carrier molecule is metabolized. Its limited availability and poorly known basic chemistry hamper the development of specific protocols for astatine-211.[30] Exploration of the fundamental chemistry of astatine is ongoing.[31] Research on the chemistry of astatine effort is focused on optimizing attachment to antibodies[32] and assuring that the constructs comply with Good Manufacturing Practices.[33]

LONGER-LIVED ALPHA EMITTERS

The longer-lived alpha emitters, radium-223 (11.4 d), actinium-225 (10.0 d) and thorium-227 (18.7 d) are suitable for clinical use. Thorium-227 is and alpha emitting radionuclide with a half-life of 18.7 days. Thorium-227 decays to radium-223 and other short-lived radionuclides in its decay chain to stable lead-207.

Investigations in mice show lymphocyte surface antigen CD70 to be a promising target for B-cell lymphomas and several solid cancers including renal cell carcinoma. Cell surface receptor CD70 targeted thorium-227 conjugate (CD70-TTC) is comprised of three components, a CD70 targeting antibody, a chelator moiety and the short-range, high-energy alpha-emitting radionuclide

SURVIVAL BENEFIT DEMONSTRATED				SUPPORTIVE CARE
AR inhibitors	Targeted alpha therapy	Chemotherapy	Immunotherapy	Supportive therapy
LHRH agonists LHRH antagonist Abiraterone Enzalutamide	Radium-223 dichloride	Docetaxel Cabazitaxel	Sipuleucel-T	Strontium-89 Samarium-153 Rhenium-186 Zoledronic acid Denosumab

INVESTIGATIONAL COMPOUNDS			
AR inhibitors	Targeted alpha therapy	Chemotherapy	Immunotherapy
Apalutamide Darolutamide	PSMA mAb thorium-227* Actinium-225 conjugates**		PROSTVAC
			Immuno-Onology
			Pembrolizumab Atezolizumab

Figure 3: Radium-223 –First in Class FDA Approved Targeted Alpha Therapy (TAT) – with Demonstrated Overall Survival Benefit in Prostate Cancer[56]

thorium-227. The conjugate showed dose dependent accumulation and growth inhibition in tumor cells.[34]

Thorium is co-produced with radium 223, and as with all the radionuclides improvements in purification and isolation are continuously being pursued.[35 - 39], as well as targeted thorium conjugates suitable for pharmaceuticals.[40]

Actinium-225, an alpha emitter with a 10 day half-life, has had a substantial amount of non-clinical work to indicate that actinium attached to appropriate antibodies and linker molecules has therapeutic potential to treat metastatic breast cancer, and bladder cancer. Actinium-225 conjugated to prostate specific membrane antigen (PSMA) shows promise but long-term toxicity studies in mice indicated that late radiation nephropathy was a dose-limiting toxicity.[41] When the PSMA conjugated construct was tested in patients with mCRPC side effects to the salivary glands were problematic.[42]

Early clinical studies showed potential for actinium-225 in glioblastoma multiforme[43] and acute myeloid leukemia.[44] Efficacy of actinium-225-labeled anti-CD33 antibody in acute myeloid leukemia and can be correlated with peripheral blast count.[44]

Importantly, radionuclides are difficult to obtain and difficult to purify. Investigators are constantly making improvements to isolation and purification technologies. Many presentations discussed these issues.[45 - 53]

SUMMING-UP

Alpha-emitters have shown substantial and highly significant efficacy with minimal toxicity in clinical conditions that are otherwise untreatable. The combination of clinical studies and pre-clinical studies suggests that alpha emitter therapy will continue to move to the clinic over the foreseeable future.

Current cancer treatment is rarely effective once the tumor has metastasized, and alpha-targeted therapy has focused on targeting metastatic spread. The eradication metastases requires a targeted therapy that is minimally susceptible to chemo- or radio-resistance, sufficiently potent to sterilize individual tumor cells and cell clusters and has acceptable toxicity. Targeted alpha-emitter therapy apparently meets these requirements. Current constraints are the lack of widespread availability of alpha-emitters, the physics, radiochemistry and radiobiological-expertise required for their clinical implementation, and concerns about potential toxicity.[54]

As we have seen at this meeting treatment is not an either/or decision. The actual picture is complicated, requiring careful evaluation of the patient and the available treatments. Layering treatments is the new paradigm. Timing is important too. The current standard treatment is to start treatment early. Treatment can start as soon as the disease progresses from asymptomatic to symptomatic mCRPC with immunotherapy to radium therapy to chemotherapy on top of continuing second generation androgen pathway inhibitors, traditional androgen-deprivation therapy, and best supportive care. Synergism amongst treatments frequently occurs.

Professor Joe O'Sullivan of Queen's University, Belfast, Ireland delivered the lunch symposium summarizing bench to bedside for targeted alpha therapy. He remarked on the ever evolving treatment for mCRPC. Docetaxel is introduced at the outset concurrent with androgen deprivation therapy (ADT). If ADT fails and the mCRPC patient is asymptomatic, sipuleucel-T, abiraterone acetate, or enzalutamide can be added to the ADT therapeutic backbone. Hence the term therapeutic layering or layering therapy.[10] As soon as the patient is mildly symptomatic, radium-223 is started and continued for 6 cycles.

New trials have shifted the paradigm again. They suggest adding abiraterone at the outset and continuing it in conjunction with radium-223 therapy.[55] The implications of the changes in the therapeutic landscape are increased overall survival and challenges in current trial endpoints.

Other new therapies are poised to emerge from on-going

trials. Actinium-225 conjugated to PMSA shows promise despite issues with side effects to be overcome. Thorium-227, the alpha-emitting parent of radium-223 theoretically could add another alpha to the tumor site. Pre-clinical studies are investigating various conjugates for thorium-227 including PSMA for prostate cancer.

The meeting ended on a positive note, calling for more personalized therapy and more ambitious treatment of metastatic castrate-resistant prostate cancer (mCRPC). What is becoming clear is that treatment decisions are not an either or process, but a careful evaluation of the patient in consideration of the patient's singular case, stage of disease and attitude. Layering therapy uses all available treatments and keeps in mind how best to treat, not only in view of treatment but in consideration of stage of disease and timing of treatment. Radiation therapy will not replace chemotherapy, ADT and other standard care, but will be used as an optimal addition to prolong life and to improve quality of life. However, the total picture is much more complex than we hoped. ■

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CONFERENCE COVERAGE

10th International Symposium on Targeted Alpha Therapy

Ishikawa Ongakudo, Hougaku Hall, Kanazawa, Japan
May 30 – June 1, 2017

TAT-10 Special Lunchtime Seminar: Radium 223 from Bench to Bedside, and Future Directions for Targeted Alpha Therapy

Dr. Joe O'Sullivan, a Professor of Radiation Oncology at Queen's College, briefly reviewed the history of radiation treatment of cancer (and prostate cancer in particular) beginning with Radium treatment only eight years after its discovery by the Curies. A landmark paper on radioactive phosphorous treatment of bone-metastatic prostate cancer was published in the journal Lancet in 1964. More recent internal treatments have concentrated on calcium analogs that are directly absorbed in the bone tumor, starting with Sr98, a beta emitter. Single agent beta emitters showed some (~50 %) palliative response but no benefit for overall survival.

The benefits of targeted alpha therapy have been recognized for some time, but the picture radically changed with the FDA approval of Ra223 dichloride in May 2013. Ra223 has an 11.4 day half-life which is a good match for distribution in the body for clinical applications. The decay chain includes four alpha emitters depositing a total of 93.5% of the decay energy. The very high linear energy transfer (LET) contributes to tumor cytotoxicity through irreparable DNA double-strand breaks.

Dr. O'Sullivan discussed the early clinical trials including three with recruits in Belfast: the BC1-04 trial with 122 mCRPC patients, the ALSYMPCA trial, and the iEAP trial. The Phase 3 ALSYMPCA trial involved 921 patients, randomly divided 2:1 into Ra223 treatment and placebo. Each group additionally also had best standard of care. All patients had confirmed mCRPC, no visceral metastases, >= 2 bone metastases, and were either post-docetaxel or unfit for docetaxel. Subgroups were identified on the basis of: total ALP (<220 U/L vs >= 220 U/L), bisphosphonate use (yes or no), and prior docetaxel use (yes or no). Patients were assessed starting at 6 months followed by 2-4 months out to 36 months. The primary endpoint was overall survival but a number of secondary endpoints (such as ALP response, PSA response, safety, and quality of life). The Ra223 patients showed a 3.6 month longer overall survival compared to placebo (14.9 vs 11.3 months). Ra223 also showed a longer time to first symptomatic skeletal event (15.6 vs 9.8 months). There was little difference in the most common side effects (anemia, bone pain, nausea, diarrhea) in the two patient populations.

Dr. O'Sullivan outlined the standard treatment paradigm of layering therapy as the disease progresses from asymptomatic to symptomatic mCRPC with immunotherapy -> radium therapy -> chemotherapy on top of continuing second generation androgen pathway inhibitors, traditional androgen-deprivation therapy, and best supportive care. Several recent trials have shifted the paradigm such that:

Docetaxel is introduced at the outset concurrent with androgen deprivation therapy. If ADT fails and the mCRPC patient is asymptomatic, Sipuleucel-T, abiraterone acetate, or enzalutamide can be added to the ADT therapeutic backbone, hence the term therapeutic layering or layering therapy. As soon as the patient is mildly symptomatic, Ra223 is started and continued for 6 cycles.

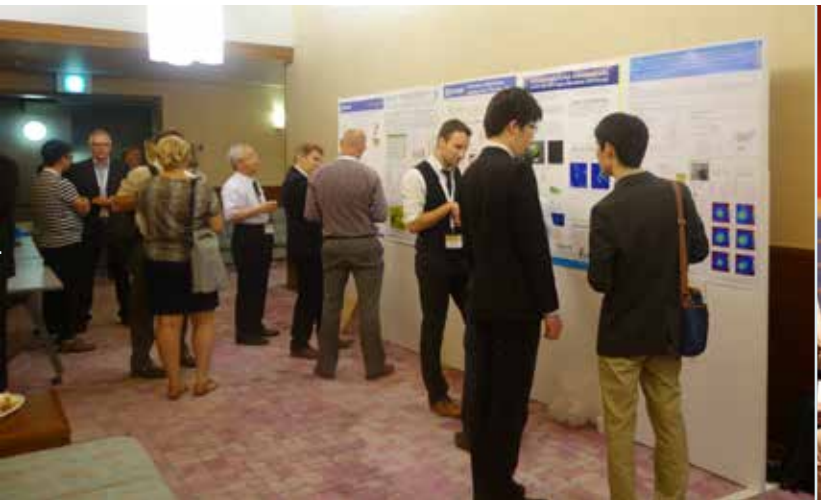
New trials could shift the paradigm again in the coming year. If successful, they suggest adding abiraterone at the outset and continuing it in conjunction with Ra223 therapy. The implications of these changes in the therapeutic landscape are increased overall survival and challenges in current trial endpoints.

Other new therapies could emerge from on-going trials. For example, Ac225 conjugated to PMSA shows great promise [see Morgenstern's contribution to this symposium] although side effects to the salivary glands are currently problematic.

In terms of new radioisotopes, Th227 with a half-life of 18.7 days is an alpha-emitting parent of Ra223 so in principle could add another alpha to the tumor site. Pre-clinical studies are investigating various conjugates for Th227 including PSMA for prostate cancer.

Dr. O'Sullivan concluded on a positive note envisioning a personalized therapy era and calling for more ambitious treatment of metastatic castrate-resistant prostate cancer (mCRP).

PRESENTED BY: JOE O'SULLIVAN, PROFESSOR OF RADIATION ONCOLOGY, QUEEN'S COLLEGE, BELFAST, AND CLINICAL DIRECTOR OF ONCOLOGY, BELFAST TRUST, BELFAST, NORTHERN IRELAND



TAT-10: Optimization of the patient dosimetry in alphatherapy

Accurate dosimetry is essential in order to deliver maximum dosage to the tumor site while minimizing the dose to other organs at risk. This study develops tools for measuring the dose from Ra223. The range of alphas is to too short to image directly in humans but the decay of Ra223 also emits gamma rays as the daughter nuclei de-excite to their ground state. These gammas can be detected. SPECT imaging of the gammas was investigated for the first time.

Phantoms containing known amounts and shapes of Ra223 in containers were used to optimize the adjustable parameters (angular and energy range) of the SPECT instrument. A 5.6ml sphere containing 20 kBq/ml showed quantitative accuracy of about 4%.

Ra223 is usually used to treat bone metastases and bone has a highly complex structure. Moreover, bone marrow is an organ at risk so the details of dosimetry are very important. A comparison was made between the alpha absorbed fractions given in ICRP Publication 30 and a Monte Carlo (MCNP6) calculation using a realistic volexized model of an adult male skeleton developed by the University of Florida. Differences of up to 50% were observed

PRESENTED BY: NADIA BENABDALLAH FROM IRSN, INSTITUTE FOR RADIOLOGICAL PROTECTION AND SAFETY, PARIS, FRANCE

TAT-10: Radium-223 in Asymptomatic Metastatic Castration Resistance Prostate Cancer Patients Treated in an International Early Access Program (iEAP)

The purpose of this study was to see if there were significant differences in asymptomatic patients at baseline compared to symptomatic patients for early treatment with Ra223. Asymptomatic was defined as no pain and no opioid use. In other selection criteria, malignant lymphadenopathy > 6cm and visceral disease were excluded.

708 patients received at least one Ra223 injection and 683 (548 symptomatic, 135 asymptomatic) received enough treatment to be evaluated. Asymptomatic patients received fewer prior treatments of abiraterone (25% vs 35%), enzalutamide (4% vs 8%), and docetaxel (52% vs 62%). Asmptomatic patients were more likely to complete the full treatment of 6 cycles of Ra223 (71% vs 55%). In addition, adverse events were less common in asymptomatic patients.

Overall survival was longer in asymptomatic patients (median 20.5 months vs 13.5 months for symptomatic). Asymptomatic patients were more likely to show alkaline phosphatase (ALP) normalization (59% vs 34%).

PRESENTED BY: JOE M. O'SULLIVAN FROM THE CENTER FOR CANCER RESEARCH AND CELL BIOLOGY, QUEEN'S UNIVERSITY, BELFAST, AND THE NORTHERN IRELAND CANCER CENTER, BELFAST, NORTHERN IRELAND

TAT-10: Changes to Alkaline Phosphatase Dynamics and Overall Survival in Metastatic Castration-Resistant Prostate Cancer Patients Treated with Radium-223 in an International Early Access Program

Identifying a reliable marker that is highly correlated with improved overall survival and reduced adverse events for Ra223 treatment would greatly aid the clinical management of metastatic castration-resistant prostate cancer (mCRPC) patients. Bone alkaline phosphate (ALP) is a marker for osteoblasts in bone tissue.

Previous studies (the ALSYMPCA trial) had shown significantly longer overall survival (OS) in patients with a confirmed ALP decline from baseline at week 12 compared to those with no ALP decline. This study continues the study of a correlation with ALP decline with improved outcomes in an international early access program (EAP).

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696 patients were recruited from 14 countries. Treatment consisted of 55 kBq/kg administered by IV every 4 weeks for up to 6 cycles. 398 patients (57%) showed confirmed ALP decline compared to 298 (43%) with no decline. Those patients with ALP decline were more likely to complete the full treatment of 5-6 Ra223. To test the positive correlation of ALP decline with OS and time to first symptomatic skeletal events (SSE), a hazard ratio (HR) was calculated from Cox proportional hazards model. The result showed both longer OS (HR of .229) and longer time to first SSE (HR of .474) for patients with ALP decline.

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TAT-10: Experimental Alpha Microdosimetry using Fluorescent Nuclear Track Detectors

This study uses a crystalline Al2O3:C,Mg Fluorescent Nuclear Track detector to measure the microdosimetry of alpha radiation to tissue.

When the heavily ionizing alpha particle traverses the crystal the ionization causes local charge-trapping defects. These defects are "frozen" in and act like fossilized markers of alpha particle track.

An irradiated crystal is subsequently scanned (in three dimensions) with a laser of appropriate wavelength. When the laser strikes a defect, the laser light is scattered and detected. In this way, a 3D picture of the alpha track is obtained and the position and angle can be reconstructed. Moreover, the laser restores the crystal defect and the crystal is ready to go again for future detections.

This technique can be used to determine the microdosimetry of sectioned tissue since the reconstructed alpha track can be extrapolated back to the tissue to determine the exact origin. Simulations of Am241 uniformly distributed in the cytoplasm of a 3D cell culture were used to determine the error in survival resulting from ignoring the microdosimetry. In some sense, the resolution is "too good" since the error in survival is far below the biological uncertainties of cell cycle RBE, OER and the targeting efficiency unknowns of alpha radionuclide carriers.

PRESENTED BY: JASPER J. M. KOUWENBERG FROM RADIOISOTOPES FOR HEALTH, DELFT UNIVERSITY OF TECHNOLOGY, DELFT, THE NETHERLANDS

TAT-10: Spectroscopic and Computational Studies of Actinium Coordination Chemistry

Ac225 is a very promising isotope for targeted alpha therapy. Production of efficient, pure conjugates would benefit from a better understanding of the basic actinium chemistry. In contrast to the tracer-level quantities of Ac225, Ac227 (half-life 22y) is available in microgram quantities which enables traditional chemical techniques. Using our stock of 150 mg (10 mCi) of Ac227, we have developed multiple spectroscopic and theoretical approaches to understand Ac coordination chemistry.

The limited supply of Ac227 requires us to fully recover the isotope after all processing and measurement thus ruling out any destructive measurements. Despite these challenges, we have completed the first X-ray absorption fine structure (XAFS) and nuclear magnetic resonance (NMR) measurements of Ac compounds. These studies contribute to understanding of Ac coordination chemistry both with simple ligands and popular chelators.

PRESENTED BY: BENJAMIN W. STEIN FROM LOS ALAMOS NATIONAL LABORATORY, CHEMISTRY DIVISION, LOS ALAMOS, NM

ASCO 2017

ASCO 2017 // JUNE 2-6, 2017 // CHICAGO, IL

The theme of the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO) was Making a Difference in Cancer Care With You. The conference attracts more than 30,000 oncology professionals from around the world with studies spanning the spectrum of cancer prevention and care, from immunotherapy and precision medicine to survivorship In this issue's Spotlight, they are selected commentaries from the top sessions in Prostate, Kidney and Bladder Cancer written by urologic oncology fellows from the University of Toronto, Princess Margaret Cancer Centre.

We welcome you to read additional conference coverage from the ASCO 2017 conference and other conferences at: www.urotoday.com/conference-highlights


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Prostate Cancer

LATITUDE: A Phase III, Double-Blind, Randomized Trial of Androgen Deprivation Therapy with Abiraterone Acetate plus Prednisone or Placebos in Newly Diagnosed High-Risk Metastatic Hormone-Naïve Prostate Cancer

Dr. Karim Fizazi and colleagues presented their much anticipated results from the LATITUDE trial at the 2017 ASCO annual meeting's plenary session. In a phase III, double-blind, randomized setting, LATITUDE tested androgen deprivation therapy (ADT) with abiraterone acetate plus prednisone (AAP) versus ADT + placebo in newly diagnosed high-risk metastatic hormone-naïve prostate cancer (PC) patients.

The de novo metastatic PC global incidence is striking: 3% in the United States and rising, 6% across Europe, 4% to 10% in Latin America, and nearly 60% in Asia-Pacific. Historically, ADT has been the standard of care, but most men with metastases progress to metastatic castration-resistant PC (MCRPC) driven by the reactivation of androgen-receptor signaling. As Dr. Fizazi observed, ADT + docetaxel is the new standard of care for men with metastatic hormone-naïve disease (with high disease burden) based on three recent randomized, controlled trials: GETUG-15[1], CHAARTED[2], and STAMPEDE[3]. As Dr. Fizazi noted, the rationale for adding AA + prednisone to ADT for metastatic hormone-naïve PC patients is threefold: (i) the mechanism of resistance to ADT may develop early, (ii) ADT alone does not inhibit androgen synthesis by the adrenal glands or PC cells, and (iii) AA + prednisone improves overall survival (OS) in MCRPC patients and reduces tumor burden in high-risk, localized PC. These points suggest that there is a role for inhibiting extragonadal androgen synthesis prior to the development of castration resistance.

The objectives of LATITUDE were to evaluate the addition of AA + prednisone to ADT on clinical benefit in men with newly diagnosed, high-risk, metastatic hormone-naïve PC. High risk was defined as meeting at least two of three criteria: (i) Gleason score of 8 or more, (ii) presence of 3 or more lesions on bone scan, and (iii) presence of measurable visceral lesions. Patients were stratified by the presence of visceral disease (yes/no) and Eastern Cooperative Oncology Group performance status (0, 1 vs. 2) and then randomized 1:1 to either ADT + AA (1000 mg daily) + prednisone (5 mg) (n = 597) or ADT + placebo (n = 602). The co-primary endpoints were OS and radiographic progression-free survival (rPFS). Secondary endpoints included time to: (i) pain progression, (ii) prostate-specific antigen progression, (iii) next symptomatic skeletal event, (iv) chemotherapy, and (v) subsequent PCtherapy. The study was conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada.

Dr. Fizazi noted that the study was designed and fully enrolled prior to publication of the CHAARTED2 and STAMPEDE3 results. For rPFS, with an alpha of 0.001 and power of 94%, 565 events (single analysis) were needed to detect a hazard ratio (HR) of 0.67. For OS, at an alpha of 0.049 and power of 85%, 426, 554, 852 (2 interim, 1 final analysis) events were needed to detect an HR of 0.81. The results presented today were from the first interim analysis.

The treatment arms were well-balanced, with over 95% of patients presenting with 3 or more bone metastases at screening in both arms. Over a median follow-up of 30.4 months, patients treated with ADT + AA + prednisone had a 38% risk reduction of death (HR 0.62, 95% confidence interval [CI] 0.51-0.76) compared with ADT + placebo. Median OS was not yet reached in the ADT + AA + prednisone arm compared with 34.7 months in the ADT + placebo arm. The OS rate at 3 years for the ADT + AA + prednisone arm was 66% compared with 49% in the ADT + placebo arm. This OS benefit was consistently favorable across all subgroups, including Eastern Cooperative Oncology Group 0 and 1 to 2, visceral metastases, Gleason score of 8 or more, and bone lesions numbering more than 10. Second, there was also 53% risk of reduction of radiographic progression or death for patients treated with ADT + AA + prednisone (median 33.0 months; HR 0.47, 95% CI 0.39-0.55) compared with ADT + placebo (14.8 months). Third, there was statistically significant improvement across all secondary endpoints for ADT + AA + prednisone: (i) time to prostate-specific antigen progression (HR 0.30, 95% CI 0.26-0.35), (ii) time to pain progression (HR 0.70, 95% CI 0.58-0.83), (iii) time to next symptomatic skeletal event (HR 0.70, 95% CI 0.54-0.92), (iv) time to chemotherapy (HR 0.44, 95% CI 0.35-0.56), and (v) time to subsequent PC therapy (HR 0.42, 95% CI 0.35-0.50).

Secondary to the above results, the study was discontinued after the first interim analysis, with adverse events being comparable in the two groups. Hypertension only rarely required treatment discontinuation, and only two patients discontinued treatment due to hypokalemia (no hypokalemia-related deaths). Two patients in each arm died of cerebrovascular events, and 10 patients treated with ADT + AA + prednisone compared with 6 patients treated with ADT + placebo died of cardiac disorders.

In conclusion, the phase III LATITUDE study demonstrated that ADT + AA + prednisone led to a significantly improved OS with a 38% reduction in risk of death, significantly prolonged rPFS (53% reduction), and improvement across all secondary endpoints. The overall safety profile was consistent with the AA + prednisone MCRPC trials. Based on these findings, Dr. Fizazi stated that "the addition of AA + prednisone to ADT can potentially be considered a new standard of care for patients with high-risk, newly diagnosed hormone-naïve prostate cancer." The full manuscript was subsequently published in The New England Journal of Medicine at the end of today's plenary session.

PRESENTED BY: KARIM FIZAZI, MD, GUSTAVE ROUSSY CANCER CAMPUS AND UNIVERSITY PARIS-SUD, PARIS, FRANCE

WRITTEN BY: ZACHARY KLAASSEN, MD, UROLOGIC ONCOLOGY FELLOW, UNIVERSITY OF TORONTO, PRINCESS MARGARET CANCER CENTRE, TORONTO, ONTARIO, CANADA

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Prostate Cancer

Adding Abiraterone for Men with High-Risk Prostate Cancer Starting Long-Term Androgen Deprivation Therapy: Survival Results from STAMPEDE

The management of newly metastatic prostate cancer (PC) has traditionally been androgen deprivation therapy (ADT), and until this decade, patients who failed ADT went on to receive chemotherapy. With the influx of new treatment options for castration-resistant prostate cancer (CRPC), there has been growing interest in assessing whether these novel therapies may be beneficial upfront. The CHAARTED study demonstrated the benefit of ADT and docetaxel chemotherapy for newly metastatic PC, particularly in patients with high-volume disease.

The STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy) Study is a large, multistage, multiarm, randomized, controlled trial being conducted in the United Kingdom to assess the utility of novel therapeutic agents in conjunction with ADT. Currently being tested are abiraterone acetate (AA), enzalutamide, zoledronic acid, docetaxel, celecoxib, and radiotherapy.

The authors presented an update regarding the AA arm of the study, which was given as a late-breaking abstract.

STUDY DESIGN:

Men with locally advanced or metastatic PC were included, with newly diagnosed patients with N1 or M1 disease, or any two of the following: Stage T3/4, prostate-specific antigen (PSA)of 40 ng/mL or more, or a Gleason score of 8 to 10. For individuals with prior radical prostatectomy or radiotherapy (RT), they could enroll if they had at least two of the following: a PSA of 4 ng/mL or more; a PSA doubling time or PSADT of fewer than 6 months; a PSA of 20 or over; and N1 disease or M1 disease.

The standard of care [SOC] (comparison arm) was ADT for 2 or more years; interestingly, treatment with RT was mandated in patients with N0M0 disease, while strongly encouraged for those with N1M0. Patients were randomized 1:1 to SOC or SOC + AA (1000 mg) + prednisone 5 mg daily. This contrasts with the prednisone 5 mg twice-a-day dosing previously used concomitantly with AA.

Duration was based on stage and receipt of RT, with those not receiving RT as well as M1 patients continued until PSA, radiographic, or clinical progression. Individuals given RT or those who opted against radiation were treated for 2 years or until progression, whichever came first.

Primary outcomes were overall survival (OS) and failure-free survival (FFS), where failure was defined as PSA failure, local failure, lymph node failure, distant metastases or PC death. PSA failure was specifically defined as a PSA fall of less than 50% (immediate failure) or in patients who had an initial PSA fall of more than 50%, a 50% rise from 24-week PSA nadir or a PSA of more than 4 ng/mL. Secondary outcome measures reported at the discussion were toxicity and skeletal-related events (SREs).

The authors noted that on trial design, comparison with control for survival had 90% power at 2.5% 1-sided alpha for a hazard ratio (HR) of 0.75, and required approximately 267 control arm deaths. Their aim was for a 25% relative improvement in OS.

RESULTS:

Over a 3-year period, they had rapid accrual of 1917 patients, who were then randomized into the two arms—957 into arm A (SOC) and 960 into arm G (SOC + AAP).

In terms of demographics, both groups were balanced: patients were predominantly metastatic (52% M1, 20% N+M0, 28% N0M0), median PSA 53 ng/dL, and 99% treated with luteinizing hormone-releasing hormone analogs. 22% were World Health Organization performance status of 1 to 2. Approximately 41% were planned for RT – 96% of N0M0 patients, 62% of the N + M0 patients. Median follow-up for the cohort was 40 months (3.3 years).

There were 262 control arm deaths, of which 82% were PC-related (cancer-specific mortality).

OS was the study's primary outcome. There was a 37% relative improvement in OS (HR 0.63, P < .0001), one of the biggest survival advantages seen in this disease space. There were 262 events in the control arm and 184 events in the SOC + AAP arm. On Forrest plot split on stratification factors, there was no significant evidence of heterogeneity based on any of the factors, which include M0/M1 status (P = .37). It should be noted that for the M0 patients, while there was improvement, the range crossed 1 (HR 0.75, 95% CI 0.48-1.18). However, the number of events was quite low during the follow-up period (44 in arm A, 34 in arm G).

FFS was the main secondary outcome. There were 535 events in the control arm and 248 in the SOC + AA arm in addition to a 71% improvement in time to failure (HR 0.29, P < .0001), with an early split in the Kaplan-Meier survival curves. Again, there was no difference in any of the subsets on Forrest plot, including M0/M1 status (P = .085).

In terms of SREs, there was a reduction in such events, particularly in the M1 cohort. There was also a 55% reduction in SREs in the M1 subset analysis.

When looking at treatment progression, 89% of the SOC arm went on to next line of therapy, while 79% of the SOC + AAP arm moved on. The SOC + AAP arm more often went on to docetaxel chemotherapy while the SOC was more likely to move on to enzalutamide or AA.

SOC + AA was relatively well-tolerated. As expected, the rate of Grades 3-5 adverse events (AEs) were higher in the SOC + AAP arm (47% vs. 33%), and were primarily cardiovascular (hypertension, myocardial infarction, cardiac dysrhythmias) or hepatic (transaminitis) in nature.

Treatment adherence was also reviewed. In the subset scheduled for 2 years of therapy, 17% stopped because of excess toxicity, but only

Prostate Cancer

1% stopped due to progression, with 69% completing treatment. In the subset scheduled for duration to progression, 52% had disease progression, while 21% stopped due to toxicity, with only 5% finishing treatment.

Based on these data, the authors concluded that the OS and FFS benefits of AAP in conjunction with ADT as first-line therapy for hormone-sensitive metastatic or locally advanced PC are significant and may well result in a change in management. AA should be considered upfront along with ADT.

During the Q & A session, the following questions were asked:

1. Dr. D'Amico: In the 28% of patients who M0, the HR of 0.75 for OS benefit (95% CI 0.48-1.18) is based on a very small number of events. Do you think that with more patients and longer-follow-up, this will reach significance?

- Dr. James: Forrest plot and subset analysis suggest that there was no significant heterogeneity based on M0/M1 status, so yes, there is likely to be a benefit in the M0 cohort as well.

2. What is the role of patient age in terms of response?

- Dr. James: Due to competing enrollment in the docetaxel arm, the number of older patients enrolled in arm G was low early on. This increased when the docetaxel arm closed enrollment, but as a result, elderly individuals' follow-up proved shorter. We can't say more today, but they have completed a meta-analysis in conjunction with LATITUDE investigators and those results will be discussed in a subsequent talk.

These results, taken in conjunction with the results of the LATITUDE trial (abstract LBA3), are compelling new evidence for the earlier utilization of AA upfront along with ADT for hormone-sensitive metastatic and advanced PC. We look forward to the meta-analysis of these two studies for more concrete results, but these initial results appear quite promising.

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Physical and Cognitive Effects of Systemic Therapy in Older Men with Prostate Cancer

Dr. Alicia K. Morgans concluded the "Disparities in Screening and Treatment of Prostate Cancer for the Older Patient" session at the 2017 ASCO meeting with an excellent talk regarding the physical and cognitive effects of systemic therapy in older men with prostate cancer (PC).

As Dr. Morgans noted, PC disproportionately affects elderly men with most cases diagnosed in men aged 65 to 74 and at a median age of 66 years. Secondly, the proportion of men exposed to androgen deprivation therapy (ADT) increases with age, particularly in men older than 80 who may have ADT as their primary therapy in upwards of over 35% of cases. According to Dr. Morgans, understanding the complications of systemic therapy for PC cancer in the elderly is critical.

It is well-established that ADT causes hypogonadal bone loss, leading to increased skeletal response to parathyroid hormone, and low estrogen, which alters the balance of osteoclast/osteoblast activity. In fact, hypogonadal bone loss is among the three leading causes of osteoporosis in men in the United States, in addition to the incidence of osteoporosis, which increases with age. ADT also leads to an elevated risk of fragility fractures. Some 20% to 25% of hip fractures occur in men worldwide, with twice the mortality of women in the six months postfracture. In the elderly, hip fracture causes loss of mobility and independence as well as increased financial burden. Given these findings, the National Comprehensive Cancer Network Guidelines recommend that patients on ADT should be supplemented with calcium and vitamin D3. Furthermore, there should be consideration for additional pharmacologic therapy if the 10-year probability of hip fracture is more than 3% or the 10-year probability of major osteoporosis-related fracture is over 20%. Finally, all patients should have a baseline bone-density test. In a Surveillance, Epidemiology, and End Results-Medicare study led by Dr. Morgans, researchers found that few men who received ADT underwent bone density testing (6%-15% over an 8-yr period), noting disparities for men who are older, African American, and/or living in areas of low educational attainment.[1]

Next, Dr. Morgans put the spotlight on cardiovascular disease (CVD) as still being the leading cause of death in the United States, including 26% of men over 65 years of age and 29% for those over 85. But whether ADT causes CVD has been highly controversial. Previous studies have suggested no increased risk for men younger than 65 years of age, but with elevated risk in men older than 65. Using data from the population-based Prostate Cancer Outcomes Study, Dr. Morgans and her colleagues noted that among 3112 patients without CVD followed prospectively, there were no increased odds of CVD with short-term ADT. However, there were significantly increased odds of CVD for patients older than 74 years of age on long-term ADT (hazard ratio 1.9, 95% confidence interval 1.0-3.5).[2] The National Comprehensive Cancer Network Guidelines suggest assessing traditional risk factors for CVD using the A (awareness of

aspirin), B (blood pressure), C (cholesterol and cigarette), D (diet and diabetes), E (exercise) approach.

There has also been concern regarding the possibility of ADT leading to diabetes mellitus. Dr. Morgans pointed out that diabetes and its complications can result in mortality in 2.8% of men older than 65 years of age and in 2.0% of men older than 85. In a Surveillance, Epidemiology, and End Results-Medicare Study from 2006, gonadotropin-releasing hormone or GnRH-agonist treatment for men with locoregional PC was associated with an increased risk of incident diabetes (adjusted HR 1.44, P < .001).[3] In Dr. Morgans' study[2], short-term ADT was not associated with the odds of diabetes. However, long-term ADT was significantly associated with the odds of diabetes in men older than 76 years of age (hazard ratio 2.1, 95% confidence interval 1.0-4.4).

Finally, dementia has been brought to light as a possible complication of ADT in recent years. Dr. Morgans observed that dementia is associated with mortality in 4.8% of men older than 65 years of age and 7.5% of patients older than 85. Four studies in the last 5 years have suggested an increased risk of dementia in varying populations of men undergoing ADT. This association is likely part of a spectrum of cognitive decline associated with the normal aging process and may occur in as little as 12 months on ADT. Currently, there are no interventions to reverse cognitive decline for this population. However, studies are being developed to address this unmet need in patients with PC. One such study is being developed by Dr. Morgans and her group, the Cognitive Effects of Androgen Receptor-Targeted Therapies for Advanced Prostate Cancer or COGCaP schema, which will enroll 50 men on abiraterone and 50 more on enzalutamide with primary outcomes being cognitive testing at baseline, 3, 6, and 12 months.

In conclusion, Dr. Morgans noted the association of ADT with numerous complications that should be considered when caring for PC survivors. Elderly men are particularly vulnerable to developing complications from ADT that increase morbidity and mortality. Importantly, this may lead to loss of mobility and independence in addition to increased financial burden.

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Clinical Implications of the 2012 US Preventive Services Task Force PSA Screening Recommendation in Prostate Cancer Diagnoses and 5-Year Survival at a Minnesota Safety Net Health Care System

Prostate-specific antigen (PSA) screening for prostate cancer (PC) has declined following the US Preventative Services Task Force (USPSTF) 2012 recommendation. Data do not exist regarding how screening rates and PC diagnoses have subsequently changed in a racially diverse patient population. Dr. Kevin Gale presented a study aiming to determine the impact of the USPSTF screening recommendation in the Hennepin Healthcare System (HHS) in the state of Minnesota.

This was a single-institution retrospective analysis of data from the authors' center electronic health record, identifying the characteristics of PSA screening and new PC diagnoses for men aged 50 and older between 2008 and 2015. Data before and after May 2012 were compared.

Nearly 22,000 patients underwent PSA screening from 2008 to 2015, with rates decreasing after May 2012 for the four largest demographics represented (P < .001). Hispanic and African American individuals were more likely to be screened when compared with White and Asian patients (P < .05). Precisely 319 PC cases were diagnosed from 2008 to 2015, with 87 (27.3%) determined by PSA screening. The number needed to diagnose one patient with PC at HHS was 137.5, and 9.5% of patients (1146 patients) had a false-positive PSA that led to further testing or a biopsy. A total of $56,090 was spent in screening costs per diagnosis of early-stage PC via screening. Patients diagnosed from screening were less likely to present with high Gleason scores (8-10) compared with nonscreening diagnoses (8% vs. 23.3%, P < .01). The 5-year survival percentage (PC mortality) was improved for those patients diagnosed by PSA screening versus the nonscreened group (100% vs. 89.3%, P < .05).

In closing, PSA screening has declined at HHS since the USPSTF recommendation against PC screening in 2012. Implementation of PSA screening in the authors' healthcare system was expensive and led to a high number of false-positives. However, the 5-year survival from PC is significantly higher when patients are diagnosed by PSA screening.

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Prostate Cancer

Clinical Implications of Genomic Sequencing in Prostate Cancer

Dr. Heather Cheng gave a short introduction before presenting an excellent summary of abstracts 5009, 5010, and 5011. Nowadays, there are many life-prolonging treatments for metastatic castration-resistant prostate cancer (MCRPC), with more in development. Genomic sequencing is advancing in tremendous steps but is still not a standard in prostate cancer (PC). It is, however, known that MCRPC has over 20% defects in DNA-repair genes (BRCA1-2, ATM, and more) and over 10% of DNA repair defects are germline (heritable). Lastly, treatment with androgen-receptor (AR)-targeted agents can select for more aggressive variants.

Dr. Cheng continued with the summary of abstract 5009—Need for re-evaluation of current guidelines based on results from germline genetic testing in prostate cancer (PC)—presented by Dr. Piper Nicolosi. A study published in The New England Journal of Medicine in 2016 of 692 men with metastatic PC demonstrated that 11.8% had germline DNA mutations.[1] The mutations were associated with autosomal-dominant cancer predisposition in men unselected for family history of age at onset of disease, with existing guidelines for genetic testing relying on a family history of cancer. Abstract 5009 analyzed 1158 patients with PC, and all had germline genetic testing for 80 genes associated with cancer (with 14 being specific for PC). The authors also analyzed whether the current genetic guidelines would have prompted genetic testing for all relevant patients. Key findings of this study included 17% having one of these genetic mutations, out of which 34% were in BRCA1 or BRCA2 and 43% in one of the other 12 prostate-specific genes, but 40% of high-risk men did not meet current guidelines criteria for genetic testing. Therefore, she indicated that new guidelines are urgently needed for genetic testing.

Dr. Cheng moved on to abstract 5010—Next-generation sequencing (NGS) of tissue and cell free DNA to identify somatic and germline alterations in advanced prostate cancer—which was presented by Dr. Michael Cheng. It is known that over 20% of MCRPC men have homologous recombination DNA repair defects—enabling them to potentially benefit from poly (ADP-ribose) polymerase (PARP) inhibitors and platinum chemotherapy. Furthermore, 5% to 10% of patients with MCRPC have evidence of microsatellite instability/hyperstimulation, potentially making them candidates for immune checkpoint inhibitors. In the study presented in abstract 5010, 1038 tumor/normal DNA pairs were prospectively analyzed from 896 PC patients using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets or MSK-IMPACT NGS assay. The authors found that 29% had DNA damage response mutations detected when somatic and germline analysis were done compared with 11% with somatic-only analysis. Therefore, the combination of somatic and germline sequencing identified more patients with potentially actionable DNA damage response alterations.

The final abstract that Dr. Cheng summarized was abstract 5011—Whole exome sequencing of circulating tumor DNA in patients with neuroendocrine prostate cancer (NEPC) informs tumor heterogeneity—presented by Dr. Himisha Beltran. NEPC is a distinctly aggressive clinical entity diagnosed with specific clinical features and treated with different chemotherapy regimens. In this study, the authors enrolled 64 CRPC patients to characterize heterogeneity (CRPC-adenocarcinoma patients vs. those with CRPC-NEPC). In addition, they did whole exome sequencing of circulating tumor DNA (ctDNA). Key findings included an 80% concordance between mutations in plasma DNA versus metastasis, ctDNA identifying relevant alterations not found in a single-site biopsy, and greater similarity in ctDNA and tumor in CRPC-NEPC than in CRPC-adenocarcinoma.

In summary, if the results of this study are validated in the future, ctDNA may aid in early diagnosis, tumor taxonomy, and direction of patients to research and treatment opportunities.

Dr. Cheng concluded by stating that genomic biomarkers to guide therapy will soon be standard for PC. To continue on the right path, she indicated that there is a need for reproducibility, measures of sensitivity and specificity, a requirement to pair genomic data with clinical outcomes, caution and discipline in interpretation of various associations, and lastly, a need to exercise care in setting appropriate expectations for patients.

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Combination of PD-L1 and PARP Inhibition in an Unselected Population with Metastatic Castrate-Resistant Prostate Cancer (MCRPC)

Novel therapies in prostate cancer (PC) are rapidly developing. Poly (ADP-ribose) polymerase (PARP) inhibitors are a group that slow down the enzyme PARP, which, in turn, results in a cell's inability to repair single-strand DNA breaks. In patients with mutations in DNA-repair genes such as a BRCA1, BRCA2, and PALB2, this second insult can lead to cell death. As over 20% of PCs have somatic DNA repair gene defects and clinical trials with PARP inhibitors have demonstrated response rates of up to 88% in patients with DRDs,[1] these inhibitors may play an important role in the management of PC.

Immune checkpoint inhibitors (ICIs) are another class of medications that have gained much interest. With efficacy established in many other malignancies, ICIs' value in PC therapy is still being determined. By blocking the immune checkpoint cascade, these agents enable a patient's own immune system to overcome cancer's immune evasion mechanism.

As PARP inhibition leads to more DNA-strand breaks and cell death, there is likely a greater increase in creation and exposure to tumor neoantigens These are proteins that can be recognized as nonself by a patient's immune system. As such, the authors of this clinical trial postulate that treatment with both an ICI and a PARP inhibitor would amplify response. They utilized olaparib (O), a PARP inhibitor, and durvalumab (D), an anti-programmed death-ligand-1 or PD-L1 antibody.

STUDY DESIGN:

This is a single-arm pilot study with a goal accrual of 25 patients, all of whom must have been previously treated with enzalutamide or abiraterone acetate. Durvalumab is given at 1500 mg intravenously every 28 days + olaparib 300 mg orally every 12 hours. The primary endpoint is progression-free survival (PFS). Secondary objectives included objective response rate, safety profile, and the correlation level of circulating tumor cells with clinical outcomes.

RESULTS:

So far, 19 patients have enrolled (median age 65 yr, median baseline prostate-specific antigen 79.67, mostly with a Gleason score of 8 or more). All were treated with enzalutamide (35%), abiraterone acetate (6%), or both (59%). Most were of Eastern Cooperative Oncology Group status of 0 to 1. About 63% had bony and visceral metastatic disease.

Grade 3/4 adverse events have included anemia (3/14, 21%), thrombocytopenia, lymphopenia, leukopenia, neutropenia, nausea, vomiting, hypertension, syncope, fatigue, urinary tract infection, and lung infection (1/14, 7% in the rest).

Seven (of 16) patients (44%) on-study for more than 2 months have had prostate-specific antigen declines of over 50%. Six-month and nine-month PFS rates are 86.7% and 57.8%, respectively. Median PFS has not yet been reached.

Patients continue to be accrued, with paired tumor biopsy and blood samples still being collected to examine for biomarkers of response in the future.

Based on data thus far, the combination of durvalumab and olaparib appears to be well-tolerated, with early oncologic outcomes showing promise.

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Identification of Low Prostate-Specific Antigen, High Gleason Prostate Cancer as a Unique Hormone-Resistant Entity with Poor Survival: A Contemporary Analysis of 640,000 Patients

Dr. David Yang and his colleagues presented results from their study that assessed patients with low prostate-specific antigen (PSA) and high Gleason score prostate cancer (PC) as a unique hormone-resistant entity with poor survival at the PC poster sessions at the ASCO 2017 annual meeting. This appears to be an understudied area and the outcomes of these patients are poorly described. The study's objective was to examine the prognostic and predictive values of a low PSA in high-grade PCtate cancer.

To perform this study, the authors used the National Cancer Database (n = 491,505) and the Surveillance, Epidemiology, and End Results program (n = 151,470) to identify 642,975 patients with localized or locally advanced PC from 2004 to 2013. Men were stratified by Gleason score (8-10 vs. ≤ 7) and PSA (≤ 2.5, 2.6-4.0, 4.1-10.0, 10.1-20.0, and > 20.0 ng/mL) for analyses. Multivariable Fine-Gray competing risks and Cox proportional regression models were used to analyze PC-specific mortality (PCSM) and all-cause mortality (ACM), respectively. There were 5.6% of patients with Gleason 8-10 tumors diagnosed with a PSA of 2.5 ng/mL or less. Using a PSA of 4.1 to 10.0 ng/mL among men with Gleason 8-10 disease as a referent, the adjusted hazard ratio (AHR) was 1.75 (95% CI 1.05-2.92) for a PSA of 2.5 ng/mL or less compared with AHRs of 1.31, 0.88, and 1.60 for PSAs of 2.6 to 4.0, 10.1 to 20.0, and more than 20.0 ng/mL, respectively. Gleason 8-10 disease with a PSA of 2.5 ng/mL or less had a much higher risk of PCSM than standard National Comprehensive Cancer Network high-risk disease (AHR 1.92, 95% CI 1.18-3.14; 47-month PCSM 14.0% vs. 10.5%). For Gleason 8-10 tumors treated with definitive radiotherapy, androgen deprivation therapy (ADT) was associated with decreased ACM for a PSA of more than 2.5 ng/mL (AHR 0.87, 95% CI 0.81-0.94), but trended toward increased ACM for a PSA of 2.5 ng/mL or less(AHR 1.27, 95% CI 0.89-1.81,P = .194; PADT*PSA interaction = .026). In contrast, PCSM for a Gleason score of 7 or less disease had an AHR of 0.32 (95% CI 0.10-1.00) for a PSA of 2.5 ng/mL or less versus AHRs of 1.13, 1.69, and 3.22 for PSA of 2.6-4.0, 10.1-20.0, and more than 20.0 ng/mL (PGleason*PSA interaction < .001), respectively.

Prostate Cancer

This is a provocatively designed study with strong methodology and a large sample size.

The authors concluded that low PSA, high-grade PC appears to be a unique hormone-resistant entity with a high risk of PCSM that responds poorly to standard treatment. Although prospective trials are warranted, based on these results these young patients should be considered for chemotherapy, novel systemic agents, and/or clinical trials.

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Targeting DNA Repair Mutations in Metastatic Castration-Resistant Prostate Cancer

Dr. Johann S. De Bono presented the final talk of the "How to Integrate Multimodal Therapy into the Management of Castration-Resistant Prostate Cancer (CRPC)" at the 2017 ASCO annual meeting session. His discussion assessed DNA repair mutations among men with CRPC.

Dr. De Bono began by posing three questions to the audience, highlighting several important points: (i) germline deleterious BRCA-mutation carriers with prostate cancer (PC) have a poor prognosis, (ii) BRCA1 deleterious aberrations are much less common than BRCA2 aberrations in metastatic PC, and (iii) deleterious BRCA2 mutations are not necessarily associated with resistance to abiraterone and enzalutamide.

Subsequently, he urged that we need to individually stratify our patient treatment, considering that what we have is not good enough. "Our patients are still dying," Dr. De Bono observed, "and most phase III trials fail. Our treatments only seem to work for a subset of patients, and the emerging biology tells us that we need to stratify. At the crux of this argument is that PC is a highly heterogeneous group of diseases, with both interpatient and intrapatient heterogeneity, which is secondary to many different genomic aberrations, specifically DNA-repair defects that encompass mismatch-repair (MMR) defects and homologous recombination-repair defects."

Based on work at Dr. De Bono's Royal Marsden Hospital, it is known that only 5% to 8% of patients with MCRPC have MMR defects, often with a relatively low mutational load. This has led to further research identifying a certain degree of programmed death-ligand-1 or PD-L1 expression in MMR-defective tumors. The recently published TOPARP-A Trial demonstrated that patients with MCRPC unresponsive to standard therapy who had DNA-repair defects responded to the PARP inhibitor olaparib[1]. Specifically, 16 of 49 patients (33%) had a response to olaparib, with 12 patients remaining on treatment for over 6 months. Germline mutations have also been extensively studied in the PC arena. Among more than 700 patients with MCRPC who have had their germline DNA sequenced, over 10% of patients have germline aberrations of DNA-repair genes.

Dr. De Bono finished up by highlighting a number of practical take-home points: (i) treatment molecular stratification of PC has arrived, specifically with immune therapy treatment in those with certain MMR-defective genes and PARP inhibitors for those with homologous recombination DNA-repair defective disease, (ii) analytically validated biomarkers should become widely available to drive stratified clinical trial accrual, and (iii) completing key clinical trials will be necessary, noting that four registered trials are currently ongoing.

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Development and Validation of a Prognostic Model for Overall Survival in Chemotherapy-Naïve Men with Metastatic Castration-Resistant Prostate Cancer from the Phase 3 Prevail Clinical Trial

While the AFFIRM trial[1] introduced enzalutamide as a treatment for castration-resistant prostate cancer (CRPC) that had failed docetaxel chemotherapy, the PREVAIL study[2,3] helped move it to the front line for newly castration-resistant patients, especially those with lower volume metastatic disease. However, both enzalutamide and abiraterone acetate have an approximately 20%-to-30% primary resistance rate. Because of the cost and potential adverse events of this medication, better patient selection should help reduce unnecessary treatment. Better understanding the outcomes of all metastatic castration-resistant prostate cancer (MCRPC) is also important.

The authors of PREVAIL, in this post-hoc analysis study, identified predictors of overall survival (OS) regardless of therapy and developed/validated a prognostic model for those with MCRPC.

Patients were randomly divided 2:1 into training (n = 1159) and testing (n = 550) sets. Demographics, disease characteristics, and OS were balanced between the training and testing sets; median OS was 32.7 months for both datasets. It was noted that treatment interaction of all the prognostic factors tested negative, which indicated that not one of them was predictive of efficacy at baseline.

Using the training set, 23 predefined potential prognostic factors (including treatment) were analyzed in a multivariable Cox model to predict OS. The final multivariable model included 11 prognostic

factors: prostate-specific antigen, treatment, hemoglobin, neutrophil-lymphocyte ratio, liver metastases, time from diagnosis to randomization, lactate dehydrogenase, 10 or more bone metastases, pain, albumin, and alkaline phosphatase. Therapy-related variables were not found to be significant.

The predictive accuracy was then assessed in the testing set, which was stratified based on risk score tertiles (low, intermediate, high) and binary (high and low) with OS analyzed using Kaplan-Meier methodology. Median OS for the low-, intermediate-, and high-risk groups in the testing set were: not yet reached, 34.2 months, and 21.1 months. In the binary mode, results were similar for low- and high-risk groups: not yet reached and 26.1 months.

The final model and its derivation are not included in the abstract, but will be provided in the final manuscript for external validation.

Clearly, there exists significant heterogeneity within the MCRPC population. As such, not all individuals likely warrant the same therapy. This prognostic model, which is based on variables routinely collected, already identified clear stratification in different patient populations.

While interesting, though, this model does not add much clinical value. A better assessment would have been an analysis of only enzalutamide-treated patients to identify predictors of response.

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Effect of Ga-68 PSMA-11 PET on Management in Patients with Recurrent Prostate Cancer

After definitive local therapy, up to 30% of prostate cancer (PC) patients have biochemical recurrence (BCR). Positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) has been shown to have a higher sensitivity and specificity compared with conventional imaging. Dr. Tom Hope presented a study that attempted to evaluate the impact of PSMA PET on the management of PC patients with BCR following local therapy (Clinical trial information: NCT02611882).

Overall, from December 2015 to October 2016, 150 patients were enrolled in this prospective trial, which evaluated the use of PSMA PET in the staging of PC patients. Inclusion criteria required a PSA doubling time of less than 12 months. Precisely 63 patients were imaged using PET/computed tomography (GE Discovery VCT) and another 63 patients were given PET/magnetic resonance imaging (MRI) (GE Signa 3.0T PET/MRI). Referring clinicians filled out pretreatment management and management forms based on the imaging results. Changes in management were graded as major, minor, no change, or unknown based on the responses.

A total of 126 forms were received, with an 84% response rate. The average PSA in the population was 5.9 ± 5.4 ng/mL with an average doubling time of 9.7 ± 11.0 months, and 49 patients had a PSA of less than 2.0 at the time of imaging. The average time between prior treatment and imaging (radical prostatectomy and/or radiation) was 5.3 ± 5.4 years, with 46 patients imaged within two years of their most recent treatment. With 43 patients having a prior prostatectomy, 41 being just prior to radiation, and 33 patients receiving both, 103 patients (82%) had disease localized on PSMA imaging. Of the 126 patients, 67 (53%) of the imaging studies resulted in a major change in management. The most common major modification was converting from active surveillance to radiation therapy (15 patients, 12%), changing from androgen deprivation therapy to radiation therapy (16 patients, 13%), and converting from radiation therapy to either active surveillance (6 patients, 5%) or to androgen deprivation therapy alone (3 patients, 2%). The end result was 10 patients (8%) having a minor change, 42 patients (33%) exhibiting no change, and 7 patients (6%) showing an unknown change in management.

The results of our surveys demonstrate a substantial impact of PSMA PET on intended patient management. The majority of changes involved converting a targeted therapy to systemic treatment, or systemic treatment to a targeted therapy. Prospective studies are warranted to determine whether directed treatment toward PSMA-avid lesions affects long-term disease outcomes.

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Bladder Cancer

Unlocking the Genome: Insights into Risk and Response in Bladder Cancer

Dr. Bishoy Faltas concluded the Bladder Cancer Genomics session with an excellent summary of four abstracts along with his take on the current status of the field.

There have been a significant number of advances in bladder cancer genomics in the past few years. With increased collaboration and development of new techniques, we are working to unlock the inner mechanics of bladder cancer and upper tract urothelial carcinoma (UTUC).

In the session, the four abstracts helped address the incidence and impact of germline mutations and somatic mutations on urothelial cancer. As Dr. Faltas reviewed genetic mutations, in and of themselves, and how they carry little clinical implication. These mutations are merely the first step in a biologic cascade that leads to a specific phenotype—disease development, drug resistance, metastatic spread, etc. Germline and somatic mutations vary significantly: germline mutations are heritable and constitutional and are determined by comparison to only a reference genome, whereas somatic mutations are nonheritable, sometimes clonal, and have to be compared with both a reference sequence and an account for germline mutations. As the germline must be better preserved from an evolutionary standpoint, the difference in the number of somatic and germline mutations is often on the order of 100X.

DNA damage repair (DDR) genes are critically important in preserving genomic integrity. Disruption in any of their pathways can lead to clinical development of malignancy, as in the case of Lynch syndrome, which is a well-known heritable genetic mutation in a DDR pathway. Indeed, Lynch syndrome and its association with urothelial carcinoma (specifically UTUC) has long been known—the Amsterdam II criteria include UTUC in familial relations.

Based on this, he addressed three main topics:

1) What is the relationship between germline mutations and urothelial carcinoma?

Work by the Memorial Sloan Kettering Cancer Center (presented by Dr. Carlo) and Dr. Faltas both demonstrated higher than expected rates of germline mutations (22%-48%) in their urothelial carcinoma (UC) cohorts. Based on this and the above knowledge of Lynch syndrome and UTUC, Dr. Faltas recommended genetic testing for germline mutations in patients with UTUC. In bladder UC, though, while he felt this may become a future standard, at this time, it should be in the context of a research protocol, and positive findings should trigger referral to a genetic counselor.

Since germline mutations can be mosaic in nature, further understanding of the pathogenic nature of the mutations must be clarified prior to clinical decision-making based on the results of these tests.

2) Can somatic mutations predict response to immunotherapy in UC?

Prior work has demonstrated that mutational load correlates with immunotherapy response, with higher mutational load more likely to lead to complete response or partial response. Mutational load also correlated to neoantigen load in UC, which may account for the clinical response.

Two of the abstracts (Drs. Teo and Iyer from Memorial Sloan Kettering Cancer Center) demonstrated that somatic DDR mutations and mismatch repair gene defects can correlate with immune checkpoint blockade clinical efficacy. Indeed, the approval of pembrolizumab for any metastatic or unresectable solid tumor with high microsatellite instability or mismatch repair deficiency is solid evidence.

3) Does tumor heterogeneity shape response to systemic therapy?

Earlier research by Dr. Faltas and colleagues demonstrated that many mutations are "private" in patients with UC, even in a single individual at different time points in treatment. Neoantigens can also arise independently. Indeed, only 7% of neoepitodes were shared among UC metastases. This heterogeneity may contribute to the nonresponse rate or failure rate in certain patients. As was discussed by Dr. Liu from the Dana-Farber Cancer Institute (Abstract 4511), a greater number of subclonal mutations is associated with worse overall survival in patients with UC who are treated with neoadjuvant chemotherapy and radical cystectomy. The same likely applies to immune checkpoint blockade response.

Dr. Faltas' prior work on genomic heterogeneity in multiple UC tissues from a single patient over the course of treatment demonstrated that even the primary tumor was a downstream branch from an earlier ancestor clone. As such, therapy based on the genomic makeup of the primary tumor or any individual metastases would likely miss significant genomic changes present in other tissues in the body.

In conclusion, UC genomics continues to rapidly evolve. As our understanding of UC biology grows, the subsequent changes have the potential to significantly impact clinical care. Take-home points are that:

1) Germline mutations are more common than previously known. Family history and screening are critically important, and germline testing should be considered.

2) Somatic DDR mutations are associated with better outcomes with immunotherapy. Better tests may help improve the selection of patients for systemic therapy or immunotherapy.

3) UC tumor heterogeneity and evolution are major barriers to durable clinical responses.

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Mismatch Repair Detection in Urothelial Carcinoma and Correlation with Immune Checkpoint Blockade Response

Dr. Gopa Iyer observed that immune checkpoint blockade (ICB) continues to be the promising new therapeutic option for many advanced malignancies, including bladder urothelial cancer (UC). With growing evidence for its use in advanced and metastatic UC, there is shifting emphasis on better patient selection.

With the knowledge that ICB ramps up a patient's own immune response by blocking tumor evasion mechanisms, there has been renewed interest in the concept of mutational load. In cancers with a high mutational burden such as UC, there are a higher number of neoantigens (or novel peptides that can be recognized as foreign) that can augment ICB response. Specifically, within each tumor type, a certain subset of patients with high mutation burdens ("mutator phenotypes") have been identified, and of these, 13% have mismatch repair deficiency signature.[1] Those with deficiency in the mismatch repair (MMR) genes are likely to have a higher mutational burden and potentially a better response to ICB.[2]

In this study, the Memorial Sloan Kettering Cancer Center group utilized an established pipeline tool called MSISensor (derived microsatellite instability [MSI] status from standard tumor-normal paired sequence data) to evaluate next-generation sequencing data from 447 tumors from 424 UC patients. Of these patients, 31% were nonmuscle-invasive bladder cancer, 27% were muscle-invasive bladder cancer, 27% were metastatic, and 14% were upper tract UC (UTUC). By assessing MSI status, the MSI score was correlated to the mutational burden and subsequently to the ICB response.

The authors classified MSI based on the following cutoffs: MSI-high (MSI-H) tumors have scores of more than 10, MSI-stable (MSS) have scores of less than 3, while patients with scores from 3 to 10 were categorized as MS-intermediate (MSI-I).

Of the cohort, 11 (3%) were MSI-H, 11 (3%) were MSI-I, and the remainder were MSS. On correlation with mutational burden, there was a strong interrelationship. Only two MSS had a high mutational burden, while all the MSI-H patients had a high mutational burden.

Next, he looked at all the MSI-H and MSI-I patients as well as the 2 MSS patients with a high mutational burden. Of the 11 MSI-H patients, nine had UTUC and nine had Lynch syndrome. Of the 11 MSI-I patients, three had UTUC and three had Lynch syndrome. One of the two patients with a high mutation load but who were also classified as MSS had Lynch syndrome.

A total of 108 patients received ICB therapy. While there was a varying response, though, all five MSI-H patients treated with ICB had a strong objective response. In fact, three patients with Lynch syndrome treated with ICB had complete responses.

Take-Home Points:

1. MSI scores are associated with mutational burden, and both may serve as potential biomarkers for ICB therapy.

2. An MSI score of 10 or more (MSI-H) has a predictive value of over 90% for MMR-deficiency(MMR-D) in UC using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets or MS-IMPACT and have a very high likelihood of Lynch syndrome—UC with MMR-D may be associated with more aggressive presentation and higher germline mutation rates of known predisposing genetic conditions (eg, Lynch syndrome). Therefore, these patients may warrant genetic testing.

3. Based on a small selected patient series, ICB therapy may provide a more durable response for MMR-D/MSI-H UC patients.

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Expanding the Actionable Landscape: Bladder Cancer Genomics—Introduction

Dr. David James McConkey gave a most interesting introductory talk on the topic of bladder cancer (BC) genomics research. During the discussion, he pointed out the current ongoing genomic revolution in bladder cancer, consisting of completion of large-scale genomic projects such as The Cancer Genome Atlas, discovery of the basal and luminal subtypes of BC, extensive research in DNA damage and repair mutations, and correlation to neo-antigens and overall mutational burden.

Significant therapeutic benefit from several treatment strategies has already been acquired. This included neoadjuvant chemotherapy for muscle-invasive BC, intravesical therapy (Bacillus Calmette-Guerin and chemotherapy) for nonmuscle-invasive BC and the discovery and application of immune checkpoint inhibitors for both muscle-invasive BC and nonmuscle-invasive BC.

According to Dr. McConkey, we are now in an era where researchers are trying to comprehend whether responses to immune checkpoint inhibitors are predictable. Extensive research is being done to understand the role of immunohistochemistry with anti-programmed death-ligand-1 in tumor tissues versus stoma tissues and the role of T-cell biomarkers. In addition, associations are being sought to neoantigen burden and mutational load.

Dr. McConkey concluded his presentation by stating the most intriguing questions to date involving BC genomics research. These include:

Bladder Cancer

1. Do some patients with BC have inherited (germline) DNA damage response (DDR) mutations?

2. Are DDR mutations associated with benefit from immunotherapy?

3. Does intratumoral heterogeneity in DDR mutations affect prognosis and/or benefit from systemic therapy?

4. And finally, are mismatch repair defects associated with benefit from immunotherapy in BC?

Hopefully, these questions can be answered in the near future and considerably advance the range, quality, and sequence of therapies given to those with BC, thereby resulting in significant clinical benefits.

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Phase 3 KEYNOTE-361 Trial: Pembrolizumab with or without Chemotherapy Versus Chemotherapy Alone in Advanced Urothelial Cancer

At the genitourinary cancer poster session at the 2017 ASCO annual meeting, Dr. Thomas Powles and colleagues presented the design of their phase III KEYNOTE-361 Trial randomizing pembrolizumab with or without chemotherapy alone in patients with advanced urothelial carcinoma (UC). Since only 5% to 15% of those with advanced BC attain long-term survival with standard first-line cisplatin-based chemotherapy, additional therapies are desperately needed. Certainly, we have seen immunotherapy with oncologic efficacy in the metastatic bladder setting,[1] with atezolizumab receiving breakthrough designation status by the FDA in June 2014. In KEYNOTE-052, first-line pembrolizumab, an anti–programmed cell death-1 antibody, demonstrated antitumor activity and acceptable safety in cisplatin-ineligible patients with advanced UC.[2]

For the phase III KEYNOTE-361 Trial, key eligibility criteria include: (i) aged 18 years or older, (ii) histologically or cytologically confirmed unresectable/metastatic UC of the renal pelvis, ureter, bladder, or urethra, (iii) measurable disease (RECIST v1.1), (iv) no prior systemic chemotherapy, (v) Eastern Cooperative Oncology Group performance status 0 to 2, and (vi) provision of a tumor sample for biomarker analyses. Patients treated with [neo]adjuvant platinum-based chemotherapy with recurrence for more than 12 months after completion will be allowed to enroll. Individuals will be randomized 1:1:1 to receive pembrolizumab 200 mg every 3 weeks, pembrolizumab + investigator's choice of chemotherapy (gemcitabine [1000 mg/m2 on days 1 and 8 every 3 weeks] + cisplatin [70 mg/m2 every 3 weeks]), or chemotherapy alone. Patients who are cisplatin-ineligible and randomized to chemotherapy will receive gemcitabine + carboplatin [area under the curve 5 every 3 weeks]. Treatment will continue until progressive disease, unacceptable adverse events, or 35 cycles of pembrolizumab in the pembrolizumab arms only. Responses will be assessed every 9 weeks for the first year and then every 12 weeks thereafter. Primary endpoints are progression-free survival (RECIST v1.1) and overall survival, while secondary endpoints include objective response rate, safety, and tolerability. Efficacy outcomes will be compared for pembrolizumab versus chemotherapy and pembrolizumab + chemotherapy versus chemotherapy.

This trial is currently ongoing and enrolling patients in 22 countries with a target enrollment of 990 people. We eagerly await the results of this important phase III study in those with metastatic UC.

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Management Strategies for Nonurothelial Bladder Cancer

Dr. Jeanny B. Aragon-Ching provided an excellent overview of current literature and management of nonurothelial bladder cancer (BC). She focused only on pure nonurothelial BC and did not include urothelial variants and mixed BCs in this talk.

While the World Health Organization recognizes eight nonurothelial BCs, there are four primary histologies that predominate. The talk spotlighted this quartet of histologies: squamous cell carcinoma (SCC), neuroendocrine tumors, bladder adenocarcinoma (urachal adenocarcinoma), and glandular neoplasms. These nonurothelial bladder cancers are rare, but often are more aggressive and may present with nonspecific/atypical symptoms, making them difficult to diagnose or treat. She highlighted some of her unpublished work using the Surveillance, Epidemiology, and End Results program or SEER dataset to look at the incidence of these histologies over a 20-year period. Compared with 215,000 cases of urothelial carcinoma, the incidence of SCC (~3000), adenocarcinoma (<1000), and neuroendocrine (<1000) BC is very low, and their 5-year survival ranged from 0.07 to 0.78%. Due to rarity, though, there are no clear guidelines for many of them.

Next, we went into the clinical presentation and management of each of the major histologies. Below, the take-home points for each are highlighted:

1) SCC

a. Accounts for 3% to 5% of BC

b. Risk factors: Chronic inflammation, infection, schistosomiasis, cyclophosphamide use

c. Two main types worldwide: Bilharzial (schistosomiasis) or nonbilharzial

- Bilharzial: Middle East/Southeast Asia, 5th decade predominant, 19% lymph node metastases, more advanced stage (but lower grade)

- Nonbilharzial: Europe/North America, 7th decade predominant, 5% to 10% lymph node metastases, advanced stage (but also high grade)

d. Due aggressive disease, radical cystectomy + lymph node dissection is standard of care

- Local failure is typical pattern of recurrence

e. No proven role for neoadjuvant chemotherapy or adjuvant chemotherapy, but not because of a lack of trials

- ITP (ifosfamide, paclitaxel, cisplatin) is the only prospectively assessed regimen[1], but it was not specific for SCC, and it was a small study

- Preoperative radiation may improve survival, but adjuvant radiation (while improving recurrence risk) does not affect survival[2]

2) Small Cell Carcinoma / Neuroendocrine

a. Fewer than 1% of all BCs, very rare

b. Predominantly male (5:1 risk)

c. Key to diagnosis is that any small amount of small cell carcinoma in the sample warrants classification as neuroendocrine

d. Diagnosis is by immunohistochemistry—chromogranin, synaptophysin, CD56

e. Classified as limited or extended, whether it is within one field of radiation therapy or not.

f. Chemotherapy is the main treatment as this is a systemic disease, with radical cystectomy or radiation only for local symptoms or control

- Neoadjuvant chemotherapy results in a high rate of pathologic downstaging and higher survival

- Regimens: Cisplatin/etoposide, carboplatin (if cisplatin-ineligible) or alternating ifosfamide/doxorubicin and cisplatin/etoposide

g. As the incidence of brain metastases is low, routine prophylactic brain irradiation is not recommended

3) Bladder Adenocarcinoma

a. Fewer than 2% of all BCs

b. Risk factors: infection, history of bladder exstrophy/repair, bladder augmentation with bowel

c. Important point to remember—search for a nonbladder primary! Requires referral to gastroenterology department for colonoscopy

d. Nonurachal: older, male, higher grade

e. Urachal adenocarcinoma (unique subset)

- Younger patients, equal male:female distribution

- Develops in the urachal remnant, but can present as a bladder tumor (dome)

- Always has enteric-type histology

- Treatment: One of the few cases of BC in which partial cystectomy is oncologically acceptable, but the key is to include en-bloc resection of the urachus and umbilicus (umbilectomy) – if not done, local recurrence in the tract is a high risk

- No clear role for nonadjuvant chemotherapy or adjuvant chemotherapy

f. For recurrent disease, chemotherapeutic regimens are similar to adenocarcinoma or SCC

- Gemcitabine + 5FU + leucovorin + cisplatin (GEM-FLP)

- 5FU + oxaliplatin (modified FOLFOX)

- ITP (similar to SCC)

She briefly summarized findings from a molecular profiling standpoint for each of the histologies. However, as these are rare, the conclusions should be taken carefully. Some key points:

1) Bladder adenocarcinoma had high ERBB2 and EGFR and, from a drug resistance standpoint, high BRCP and MRP1

2) Urachal adenocarcinoma had an association with high microsatellite instability, and the genes most commonly mutated were KRAS, NRAS, BRAF

While series in small cell and SCC are increasing, the studies remain quite small. Early next-generation sequencing analysis has promising results, but nothing definitive yet.

Lastly, Dr. Aragon-Ching highlighted recent work that uses targeted immunotherapy. Abstract 293 (A. Apolo et al) demonstrates efficacy of cabozantinib + nivolumab +/- ipilimumab, but specific efficacy was noted in the nonurothelial subsets. Upcoming trials include the ALLIANCE Trial and the Southwest Oncology Group's DART trial, both of which specifically target rare genitourinary cancers.

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Bladder Cancer

Health-Related Quality of Life of Pembrolizumab Versus Chemotherapy for Previously Treated Advanced Urothelial Cancer in KEYNOTE-045

Pembrolizumab is one of five FDA-approved immune checkpoint inhibitors for patients with metastatic or advanced urothelial carcinoma who have failed platinum-based chemotherapy. The KeyNote 045 Trial[1] demonstrated a 2.9-month median overall survival benefit compared with second-line chemotherapy with acceptable toxicity for individuals treated with 200 mg of intravenous pembrolizumab every 3 weeks until treatment progression (Overall survival, hazard ratio 0.73).

In this abstract, the Dr. Ronald De Wit and his co-authors focused instead on the health-related quality of life (HRQoL) outcomes in the KeyNote 045 Study, with specific emphasis on whether HRQoL impact was a marker for treatment efficacy. This was a prespecified secondary planned analysis at the time of study completion.

STUDY DESIGN:

The European Organisation for Research and Treatment of Cancer's QLQ-C30 HRQoL instrument was administered electronically at cycles 1 to 4, then every 2 cycles for up to 1 year, and 30 days after discontinuation. The key HRQoL endpoints were 1) change from baseline to week 15 and 2) time to deterioration (defined as 10 or more points of decrease from baseline) in the QLQ-C30 global health status/quality of life score. HRQoL was only assessed in patients who received 1 or more doses of assigned study treatment and completed 1 or more HRQoL instruments.

Of note, programmed death-ligand-1 (PD-L1)-positive status was determined by a tumor programmed cell death-1 ligand combined positive score (the percentage of PD-L1-expressing tumor and infiltrating immune cells relative to the total number of tumor cells) of 10% or more.

RESULTS:

Of the 542 patients in the original study, 520 met inclusion criteria for the HRQoL evaluation, which is much higher than other similar assessments. Baseline responses were similar between both arms, and there was an 88% compliance rate for the week-15 survey. Key findings from the study were:

1. From baseline to week 15, scores were stable for pembrolizumab (n = 266), but worsened for the second-line chemotherapy patients (n = 254)

   a. The difference in means between arms was 9.05 (95% confidence interval 4.61-13.48; P < .001)

2. At week 15, patients who were PD(-) status had improved scores with pembrolizumab but still had worsened scores with 2nd-line chemo (mean +5.97 vs −4.31), while pts with PD(+) status had less worsening with pembrolizumab (mean −3.54 vs −13.95) compared with 2nd line chemo)

3. On Kaplan-Meier analysis, time to deterioration was prolonged with pembrolizumab (median 3.5 mo vs 2.2 mo, nominal 1-sided P = .002) compared with second-line chemotherapy

4. Rates of improvement (defined as 10 or more points of increase from baseline) at week 15 were 31.2% with pembrolizumab and 22.0% with second-line chemotherapy; rates of deterioration were 28.9% and 40.6%, respectively

5. Importantly, patients in both arms who did not have progression of disease did experience improvement from baseline (in the pembrolizumab arm) or at least less of a decrease (chemotherapy arm).

Based on the original study results demonstrating overall survival benefit and these results demonstrating HRQoL superiority, the authors suggest that pembrolizumab should become a standard of care. Importantly, they had a high survey completion rate, thereby strengthening their findings. Interestingly, PD-L1-positive patients did have a worsening of HRQoL, but less so than with second-line chemotherapy. While it would have been interesting to correlate HRQoL outcomes with clinical efficacy, the authors may have to consider this for future studies.

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Cabazitaxel in patients with locally advanced or metastatic transitional cell carcinoma who developed disease progression within 12 months of platinum based chemotherapy: Results of a phase II trial—CAB-B1.

In the past 1 year, five different immune checkpoint inhibitors have been approved by the FDA approved for the treatment of metastatic or advanced urothelial carcinoma (UC): atezolizumab, durvalumab, nivolumab, pembrolizumab and most recently avelumab. However, while the initial enthusiasm for this new class of therapies appears warranted, further long-term studies and confirmatory studies are required. Importantly though, each of these drugs has an objective response rate of approximately 20%, indicating that 80% of patients do not have a strong response. So, while studies on ICI's should continue, additional treatment options for this patient population are needed.

As second-line chemotherapy options are currently limited, further research into newer agents may provide better salvage treatment options. Cabazitaxel is the fourth taxane to be approved for cancer therapy, and is a microtubule inhibitor like the others. It has had demonstrated success in the management of castration-resistant prostate cancer, and is currently an approved option for CRPC patients who have failed docetaxol chemotherapy.

In this study, however, the United Kingdom group assesses cabazitaxel efficacy in patients with metastatic or advanced urothelial carcinoma (mUC) who have failed platinum-based chemotherapy (CT), based on positive in-vivo studies in resistant UC cell lines.

STUDY DESIGN:

This a single-center phase II trial in patients with advanced or metastatic UC who have been treated with platinum-based CT, but who have recurred within 12 months of CT completion. Treatment arms were best supportive care (BSC) or Cabazitaxel (CAB; 25mg/m2 q3 weeks for 6 cycles). Primary outcome was overall response rate (ORR) using RESIST. Secondary outcomes were Progression Free Survival (PFS), Overall Survival (OS), Quality of Life assessment, safety and tolerability. As a two-stage design was generated, this first stage required only 20 patients.

RESULTS:

In a 3-year period, 20 patients were randomized (10 to each arm) – the cohort was primarily male, median age 68, and most had recurred within 6 months of the last CT cycle. For the BSC arm, 9 patients received paclitaxel and 1 received radiotherapy.

Only 8 of the 19 patients undergoing chemotherapy completed the chemotherapy course – 3 in the CAB arm, 5 in the BSC arm. Main reason for discontinuation of cabazitaxel was adverse events, and 5 cycles that were administered were dose reduced. There were 10 serious adverse events due to toxicities that resulted in hospitalization were experienced by 6 patients on the cabazitaxel arm.

Since 6 patients in each arm had completed 2/3 of the CT cycles, these patients were compared for response – 2 CAB patients had evidence of objective response, while only 1 in the BSC arm.

In the time frame, 14 patients (70%) died of disease – 8 in the CAB arm, 6 in the BSC arm.

Median OS was 5.6 months for CAB pts and 8.2 months for BSC pts. Median PFS was 4.4 months for CAB pts and 4.1 months for BSC pts.

It is important to note, the authors had significant trouble recruiting even the 20 patients needed for the first phase. They will need an additional 76 patients to detect difference in ORR between 5-30%. This will likely be difficult to achieve due to poor clinical status of many of these patients.

Based on preliminary results, the authors conclude that CAB has promise as a second-line option in patients who have early failures of platinum-based chemotherapy for metastatic or advanced UC. However, it should be noted that there was significant drug cessation due to adverse events.

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Kidney Cancer

Sequence and Decision-Making in the Treatment of Renal Cell Carcinoma

Dr. Neeraj Agarwal provided an excellent and thorough talk highlighting sequence and decision-making in the treatment of renal cell carcinoma at the session, "Evolving Treatment Paradigm in Renal Cell Carcinoma," at the ASCO 2017 annual meeting.

Dr. Agarwal began by highlighting the poor prognostic factors associated with response to vascular endothelial growth factor inhibitors, namely (i) a Karnofsky Performance status of less than 80%, (ii) time to therapy interval of under 1 year, (iii) anemia, (iv) hypercalcemia, (v) neutrophilia, and (vi) thrombocytosis. These factors have subsequently been translated into the International Metastatic Database Consortium prognostic criteria: favorable (0 factors, median overall survival [OS] 43 mo), intermediate (1-2 factors, median OS 22 mo), poor risk (3-6 factors, median OS 8 mo).

In the first-line targeted therapy for metastatic clear cell renal cell carcinoma, there are many agents, including sunitinib, pazopanib, and bevacizumab + interferon. Specifically for poor-risk patients, temsirolimus is considered the most appropriate agent. As mentioned in Dr. Ulka Vaishampayan's talk, high-dose interleukin (IL)-2 should also be considered as first-line therapy, even in the targeted therapy era. Certainly there are upcoming new first-line treatments, including cabozantinib, which leads to Von Hippel-Lindau inactivation, upregulation of MET, vascular endothelial growth factor, and AXL, subsequently leading to inhibition of tumor progression, growth, and invasion.

The recently published CABOSUN Trial[1] demonstrated that cabozantinib derived a significant benefit in progression-free survival (PFS; 8.2 vs. 5.6 mo, hazard ratio [HR] 0.66, 95% confidence interval [CI], 0.46-0.95) and objective response rate over sunitinib in the first line, specifically for patients with intermediate- or poor-risk metastatic RCC. Results of the IMmotion 150 trial of atezolizumab + bevacizumab versus atezolizumab versus sunitinib were presented at the meeting (Abstract 4505).

Additionally, there have been multiple clinical trials assessing targeted therapy in the second line after first-line disease progression. The AXIS trial was published in 2011, assessing axitinib versus sorafenib, reporting that axitinib resulted in a significantly longer PFS (6.7 vs. 4.7 mo; HR 0.67, 95% CI 0.54-0.81) compared with sorafenib.[2] The METEOR Trial (cabozantinib vs. everolimus) demonstrated a significantly improved PFS with cabozantinib (median PFS 7.4 vs. 3.9 months; HR 0.51, 95% CI 0.41-0.62).[3] An updated analysis of this trial demonstrated a continued benefit of cabozantinib regarding OS (median 21.4 vs. 16.5 mo; HR 0.66, 95% CI 0.53-0.83).[4]

Lenvatinib was also tested in the second line, specifically lenvatinib + everolimus and lenvatinib alone and found that PFS for patients treated with combination therapy (HR 0.40, 95% CI 0.24-0.68) and lenvatinib alone (HR 0.61, 95% CI 0.38-0.98) had improved compared with everolimus alone.[5] Finally, in a landmark study incorporating immunotherapy, nivolumab versus everolimus (CheckMate 025) showed an improved OS for patients taking nivolumab (median OS 25.0 vs. 19.6; HR 0.73, 95% CI 0.60-0.89).[6] The challenge with selecting an appropriate second-line therapy is that we do not have validated biomarkers, although programmed death-ligand-1 or PD-L1 expression has been tested in the CheckMate-025 Trial.

In a subset analysis of the METEOR Trial looking at patients with bone metastasis, individuals treated with cabozantinib had an improved PFS compared with those treated with everolimus (7.4 vs. 2.7 mo, HR 0.33), suggesting that patients with bone metastasis may benefit from cabozantinib therapy. As Dr. Agarwal noted, there may be additional considerations at play for selecting second-line therapy, including (i) oral vs. intravenous administration, (ii) co-pays for oral agents, and (iii) physician comfort with the agent being administered.

Dr. Agarwal concluded with excellent summary algorithm slides for sequencing possibilities in the current era. After first-line therapy with either sunitinib, pazopanib, or bevacizumab + interferon, it is reasonable to consider either nivolumab, cabozantinib, lenvatinib-everolimus, or axitinib in the second-line setting. If patients are treated with first-line high-dose IL-2 or other immunotherapy agents, potential second-line medications include axitinib, pazopanib, or sunitinib. Finally, if patients are treated with first-line temsirolimus, possible second-line agents include nivolumab, cabozantinib, sunitinib, and pazopanib. He finished with a pertinent statement, "Clinical trials should be offered for every line since cure is unlikely with current therapy."

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Current Therapeutics of Kidney Cancer: Landmark Trials

Dr. Ulka Vaishampayan provided an excellent walk down memory lane, highlighting the landmark trials in kidney cancer over the last 20 years at the ASCO 2017 annual meeting session, "Evolving Treatment Paradigm in Renal Cell Carcinoma."

Dr. Vaishampayan started by highlighting data from the Surveillance, Epidemiology, and End Results or SEER Program suggesting that although the incidence of kidney cancer has increased over the past 40 years, the mortality rates have essentially stayed the same over this time period. Interleukin (IL)-2 has been approved for treatment of advanced renal cell carcinoma (RCC) since 1992, and results of 255 patients who received high-dose IL-2 therapy demonstrated an objective response rate of 14%, a complete response (CR) rate of 5%, and a partial response (PR) rate of 9%.[1] Data from the PROCLAIMSM Trial of 352 patients receiving targeted therapy prior to or following high-dose IL-2 demonstrated 4% CR, 13% PR, 39% stable disease, and 43% progressive disease with IL-2, showing a clinical benefit for patients who progressed on targeted therapy.[2] Conclusions from these IL-2 studies include the fact that certain patients treated with IL-2 will have a CR + PR of approximately 15%. However, the majority of these patients are at intermediate risk and not at high risk. Furthermore, despite the toxicities of IL-2, they are predictable and manageable, and therapy is remarkably time and cost-effective.. Dr. Vaishampayan then observed that based on a meta-analysis of phase III trials of cytoreductive nephrectomy in the interferon era, patients derive a statistically significant survival benefit.[3] However, as Dr. Vaishampayan noted, based on recent SEER data, only one-third of patients receive cytoreductive nephrectomy.

The early to mid-2000s saw the development of tyrosine kinase inhibitor therapy. In 2007, Escudier et al. demonstrated that sorafenib compared with placebo prolonged progression-free survival (PFS) in patients with advanced RCC.[4] Additional trials that year also demonstrated improved PFS for sunitinib compared with interferon-alfa[5] as well as temsirolimus compared with interferon-alfa, particularly in patients with poor prognoses.[6] In 2013, we saw the COMPARZ trial of pazopanib versus sunitinib in the first line for metastatic RCC, demonstrating comparable efficacy between the two agents (median OS: sunitinib 29.3 mo vs. pazopanib 28.4 mo), although with improved tolerability with pazopanib.[7]

There is currently a plethora of phase III trials for second-line therapy for patients with metastatic RCC that have been reported in the past few years. In 2015, the METEOR Trial (cabozantinib vs. everolimus) reported that PFS was longer in the cabozantinib arm compared with everolimus (hazard ratio [HR] for death 0.67, 95% CI 0.51-0.89).[8] A recently updated analysis of these data demonstrated a better overall survival, delayed disease progression, and an improved objective response rate for cabozantinib.[9] Finally, Motzer and colleagues assessed lenvatinib + everolimus and lenvatinib alone and found that PFS for patients treated with combination therapy (HR 0.40, 95% CI 0.24-0.68) and lenvatinib alone (HR 0.61, 95% CI 0.38-0.98) was improved compared to everolimus alone.[10]

To conclude, there are many novel immune therapy trials ongoing, but the landmark trials have established efficacy of multiple therapies in advanced RCC. As Dr. Vaishampayan noted, with multiple therapies available, a discussion of risk/reward ratio should occur with each patient. Certainly, she and her associates have hopes that single biomarker-driven therapy may eventually be possible. However, this type of treatment is not currently available to ultimately guide precise management.

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Emerging VEGF-I/O Combinations: Efficacy and Toxicity

Dr. Hans Hammers provided an excellent summary of abstracts 4504-4506 (Abstract 4504 TK Choueiri et al, Abstract 4505 MB Atkin et al, Abstract 4506 S. Chowdhury), all of which address emerging vascular endothelial growth factor and immunotherapy combinations. The rationale for combination therapy can be traced back to the CheckMate 025 trial[1], in which nivolumab was tested against everolimus as a second-line therapy for advanced renal cell carcinoma.

Nivolumab had a higher objective response rate (ORR) (25% vs. 5%) and fewer Grade 3-4 adverse events (AEs) (19% vs. 37%), without necessarily improving progression-free survival. Based on this, the rationale exists for potential combination therapy. However, balancing AEs for survival benefit is often the limiting factor.

Dr. Hammers had an interesting commentary on the possibility that combined therapy may not necessarily be synergistic in the traditional sense (targeting complementing pathways), but that they may help push cancer cells toward cell death. The balance between cell death and cell growth is that normal cells are significantly altered, favoring cell growth in cancer. However, while immune therapies shift that balance slightly toward cell death (in some patients), and targeted therapies balance out cell death and cell growth (static therapy), the combination may shift more toward cell death.

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He began by reviewing Abstract 4506 by Chowdhury et al. In this study, he congratulated the authors for their determination and, along with those authors, made it clear that the combination of pembrolizumab and pazopanib should not be considered for further studies due to hepatoxicity and side-effects profile. However, this does serve as a very important example of the significant toxicity from combined therapy. The study, in conjunction with CheckMate 016, which compared nivolumab with either sunitinib or pazopanib, demonstrated that non-specific tyrosine kinase inhibitors (TKIs) may not be appropriate for combination therapy. Not all TKIs are equivalent! There most definitely exists a case for more selective TKIs as combination agents with immune checkpoint inhibitors.

The study by Choueiri et al (Abstract 4504) that uses avelumab and axitinib (currently a second-line TKI) demonstrated very minimal hepatotoxicity. The safety profile of the combination appeared acceptable in this phase 1/2 study, but Dr. Hammers did note that approximately 8% of patients still had Grade 3 hepatotoxicity, which was more than the expected 1% for axitinib alone. While there was one immune-mediate death (myocarditis), the overall safety profile appeared acceptable. Particularly when taken in the context of its early clinical outcomes, this combination seems to be promising. With a confirmed ORR of 58.2%, this teaming is significantly better than what monotherapy alone can offer. However, as this is a preliminary study, much longer follow-up is needed to ensure durability of response.

This study also highlighted the success gained by using a more selective TKI such as axitinib and tivozanib or multiselective TKIs such as cabozantinib and levantinib. These may offer better oncologic benefit with more acceptable AE profiles than nonselective TKIs such as pazopanib and sunitinib.

Lastly, Dr. Hammers reviewed Abstract 4505 by Atkin et al, in which the authors assessed the combination of atezolizumab with bevacizumab (vascular endothelial growth factor inhibitor) versus sunitinib alone. He congratulated the authors on the novel study design that allowed for crossover after monotherapy and noted that the ORR of combination therapy compared with monotherapy alone was not very different: 32% for combination therapy and 25% for atezolizumab monotherapy. Matched with 58% axitinib/avelumab ORR and a 71% pembrolizumab/axitinib ORR, this does not appear to be as effective.

However, an interesting component of this group's study is their sequencing of patients and identifying a potential biomarker of response. Specifically, the identification is that patients with high T-effector cell expression and high levels of myeloid inflammation have a better response to bevacizumab addition than do patients with high T-effector cell expression. Therefore, low levels of myeloid inflammation may help guide the addition of bevacizumab in the future. Dr. Hammers observed that it was unclear how independent of programmed death-ligand-1 expression this new biomarker was, so he indicated that there is a definite need for further evaluation.

Particularly beneficial about his assessment of how all these combinations will affect the current Kaplan-Meier curve for immunotherapy was that now, 70% to 80% of patients have an early failure rate, but there is a long-tail (durable response) for the 20% to 30% that do respond. Ideally, these therapies maintain a durable response, but raise the response rate and the overall survival.

At this time, without longer follow-up, we do not know if these new combinations merely increase the early ORR yet have no effect on progression-free survival or overall survival. However, novel combination therapies are promising so long as they balance against the side-effects profile of the treatments themselves.

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Phase III Trial of Adjuvant Sunitinib in Patients with High-Risk Renal Cell Carcinoma: Validation of the 16-Gene Recurrence Score in Stage III Patients

In the last year, the S-TRAC randomized, controlled trial[1] demonstrated that patients receiving adjuvant sunitinib versus placebo for high-risk renal cell carcinoma (RCC) have improved disease-free survival (DFS). Similarly, at the same session, it was reported that those treated with adjuvant pazopanib (800 mg) may also have improved DFS.[2] However, selecting which patients may benefit from adjuvant treatment has been largely unknown.

At the ASCO 2017 annual meeting's genitourinary cancer oral abstract session, Dr. Bernard J. Escudier and his colleagues presented their results of a 16-gene Recurrence Score for stage III RCC patients to further characterize which ones may benefit from adjuvant therapy. The 16-gene Recurrence Score was previously developed and validated to predict risk of recurrence of RCC after nephrectomy in two cohorts of stage I-III patients.[3] The study's objective was to offer further validation of the Recurrence Score in high-risk, stage III patients from S-TRAC.

This study was prospectively designed with prespecified genes and an analysis plan that utilized primary RCC tissues from 193 stage III evaluable patients from S-TRAC. Gene expression was quantitated using reverse transcriptase-polymerase chain reaction, with time to recurrence (TTR) and DFS analyzed using Cox proportional hazards modeling. Baseline characteristics were similar in the sunitinib and placebo arms and in patients with and without gene expression data. The Recurrence Score predicted TTR (hazard 2.5-4.2) and DFS (hazard ratio 2.3-3.8) in both the treatment and placebo arms, with stronger results noted in the placebo arm. The authors also noted that the interaction of Recurrence Score with treatment was not

significant (TTR P = .19; DFS P = .22), but the number of adverse events was relatively low.

To conclude, the prognostic value of the Recurrence Score gene assay was confirmed in the high-risk, stage III S-TRAC patients, with the strongest association observed in the placebo arm. Since the Recurrence Score has now been validated in multiple studies, these results may help identify individuals at high risk who may derive added benefit from adjuvant therapy. Given the side-effect incidence and severity in the previous randomized, controlled trials with adjuvant treatment, having additional predictors to select patients who may benefit from adjuvant therapy is significant.

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Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo after Nephrectomy in Patients with Locally Advanced Renal Cell Carcinoma (RCC) (PROTECT)

On the heels of two randomized, controlled trials (RCTs) recently published assessing adjuvant tyrosine kinase inhibitors in the setting of patients treated with radical nephrectomy for locally advanced renal cell carcinoma (RCC),[1,2] Dr. Robert J. Motzer and his colleagues presented their findings of another phase III RCT evaluating adjuvant pazopanib versus placebo in these high-risk patients. ASSURE[1] randomized patients 1:1:1 to adjuvant sunitinib versus sorafenib versus placebo, demonstrating no survival benefit for either medication compared with placebo. However, S-TRAC[2] randomized patients to adjuvant sunitinib versus placebo, finding that median duration of disease-free survival (DFS) was significantly longer in the sunitinib group compared with placebo.

Those enrolled in PROTECT (n = 1538) had either resected pT2 (high-grade) or pT3 or larger clear cell RCC after nephrectomy and were randomized to pazopanib versus placebo for 1 year. The starting dose (800 mg) following treatment of 403 patients was lowered to 600 mg to improve tolerability. Subsequently, the primary endpoint was changed to DFS with pazopanib 600 mg (n = 1135), which was performed after 350 DFS events in an intention-to-treat (ITT) analysis. A second DFS analysis was performed after an additional 12 months, and secondary endpoints included (i) DFS with ITT for patients receiving pazopanib 800 mg, (ii) ITT for all patients, and (iii) safety outcomes. Disease characteristics were similar between arms, and the results of the primary analysis (DFS ITT for patients receiving pazopanib 600 mg) was not significant (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.70-1.06). ITT DFS for patients given 800 mg (HR 0.69, 95 %CI 0.51-0.94) and all patients (HR 0.80, 95% CI 0.68-0.95) was significant, leading to a 31% and a 20% risk reduction, respectively. On updated analysis, the 600 mg dose was still insignificant, but the 800 mg dose showed continued risk reduction (HR 0.66, 95% CI 0.49-0.90). There was no difference in overall survival among any of three analysis groups. However, given the prematurity for this endpoint, the final OS analysis will be performed in April 2019. Increased alanine transaminase (ALT) and aspartate transaminase (AST) were the most common adverse events leading to treatment discontinuation in the pazopanib 600 mg (ALT 16% and AST 5%) and 800 mg (ALT 18% and AST 7%) cohorts.

This study demonstrated a 31% recurrence reduction for patients treated with 800 mg pazopanib in ITT analysis, but this was a secondary objective of the study. The research did not meet the primary DFS endpoint for 600 mg pazopanib and is not recommended for adjuvant therapy following resection of locally advanced RCC.

CLINICAL TRIAL: NCT01235962

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The Dynamic Landscape of Renal Cell Carcinoma Biomarkers: Can We Predict Prognosis, Treatment Response, and Outcome?

Dr. James Brugarolas provided a succinct summary of the key points, highlights, and potential limitations of the three excellent ASCO 2017 abstracts (Abstract 5422 George et al, Abstract 5423 Voss et al, and Abstract 5424 Carlo et al). He began with Abstract 5424, in

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which the authors assessed the prevalence of cancer susceptibility germline mutations in patients with advanced renal cell carcinoma (RCC).

Using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets or MSK-IMPACT next-generation sequencing prospective study, the researchers identified 226 patients over a 1-year period. Specifically, Dr. Brugarolas commented that the population had a relatively high proportion of young (<45-year-old) patients, individuals with bilateral disease, and non-clear cell histology, which may not represent a typical practice. The authors identified 38 germline mutations in 38 patients, and CHEK2 was the most common (24%). Other common mutations included BAP2 and APC, while there was a smaller proportion of DNA damage repair gene mutations. Importantly, germline mutations were not significant predictors of presentation.

The colleagues next assessed how many of these mutations would have been missed by American College of Medical Genetics or ACMG criteria for genetics referral. Current guidelines recommend referral for early-onset or aggressive clear cell RCC, any nonclear cell histology, or any clinical history consistent with genetic syndromes. About 62% of clear cell RCC patients with germline mutations would have been missed.

Dr. Brugarolas' main input regarding their conclusions for this abstract were as follows:

1. Their population may not be representative of the general population presenting with advanced RCC;

2. ACMG criteria need to be updated in the areas of nonclear cell RCC and inclusion of unclassified RCC;

3. There is a lack of correlation with clinical criteria that is likely traceable to sample size;

4. CHEK2 mutation was associated with an increased risk of RCC and a loss of heterozygosity in the tumor;

5. BAP2 mutations were seen in both clear cell and nonclear cell patients, which differs from prior study results. Two of this cohort's patients had both clear cell RCC and nonclear cell RCC, but only one nonclear cell case was clearly independent.

He then moved on to Abstract 5423, in which the authors looked back at the COMPARZ Trial, which compared pazopanib with sunitinib in the setting of advanced or metastatic RCC. They utilized the patient data and available tissue to correlate PBRM1 and BAP1 mutation rates with clinical outcomes, regardless of treatment arm. RNA and DNA data were available for 352 of the patients. Of those people, 15% had BAP1 mutation and 44% had PBRM1 mutation. Dr. Brugarolas observed that there was some relationship between these genes that may be confounding some of the study's results, so he requested secondary analysis after abstract submission to clarify.

The original study found that PBRM1 mutation was associated with improved PFS and OS, but the groups were unbalanced for BAP1 mutations. A PBRM1 mutant tumor is less likely (odds ratio 0.3) to harbor a BAP1 mutation than wild type. They subsequently noted reduced progression-free survival (PFS) and overall survival (OS) with BAP1 mutations.

A prior study in Nature Genetics in 2012 (Pena-Lops et al) identified four molecular subtypes based on different combinations of BAP1 and PBRM1 mutations associated with different clinical outcomes. To compare, the authors, on Dr. Brugarolas' request, did the secondary analysis. Four distinct clinical outcomes were noted, which were similar to the results of the 2012 study. PBRM1-BAP1- patients had significantly worse PFS and OS. Subsequent analysis linking angiogenic signature demonstrated that high angiogenic signature was associated with improved PFS and OS.

His main input regarding their conclusions for this abstract were as follows:

1) Acquired mutations in PBRM1 and BAP1 are common mutations in advanced RCC;

2) PBRM1 and BAP1 mutations are not independent and should be considered together;

3) Loss of PBRM1 appears to enhance the proangiogenic microenvironment, but

Dr. Brugarolas thought this to be provocative, although there appear to be significant limitations to the dataset;

4) It may be more interesting to look at treatment response prediction based on PBRM1/BAP1 mutation

Lastly, he discussed Abstract 5422, in which the authors looked at the association of hepatocyte growth factor (HGF) levels (during therapy) to clinical response in patients treated in the ALLIANCE CALGB 90206 study. In that research, individuals were given interferon-alpha or IFN- +/- bevacizumab for advanced RCC. They found that baseline HGF levels were predictive of OS, with high HGF levels predicting worse OS. Importantly, the absolute HGF level at 4 weeks and a decrease in HGF levels at 4 weeks were prognostic in multivariable analysis.

Dr. Brugarolas did not have much to add to the authors' conclusions. They extended the work of others by demonstrating that HGF change during therapy has prognostic value. HGF levels that remain low on therapy have the best OS and may be treated with vascular endothelial growth factor-selected therapy. HGF levels that start high and stay high on therapy potentially identify patients who may need HGF-MET axis-targeted therapy.

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Can Subgroup Analyses Identify Enrichment Strategies for Adjuvant RCC Studies?

Dr. Daniel Heng from Calgary, Canada provided the discussant talk following presentation of "Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT)"[1]) and "Phase III trial of adjuvant sunitinib in patients with high-risk RCC: Validation of the 16-gene Recurrence Score in stage III patients[2].

Dr. Heng started by highlighting the three reported TKI adjuvant trials: (i) ASSURE, which found no disease-free survival (DFS) or overall survival (OS) benefit for either sunitinib or sorafenib among clear cell and non-clear cell RCC ≥T2Gr3/4 patients[3]; (ii) S-TRACT, which found a DFS benefit (1-2 years, HR 0.75), but no OS benefit with the immature data (and underpowered) among patients with clear cell RCC ≥T3 disease[4]; and (iii) PROTECT, which found no DFS or OS for adjuvant pazopanib among patients with clear cell RCC ≥T2Gr3/4 patients[1]. Indeed, adjuvant therapy for resected localized RCC remains controversial, with low uptake. It is difficult to know if high risk subgroups may benefit more from adjuvant TKI therapy.

Dr. Heng feels that the optimal adjuvant therapy population has the following characteristics: high recurrence score, clear cell histology, and high stage. Adequate dosing for these patients is also crucial. As highlighted in the PROTECT Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 survey, tolerability of pazopanib, similarly to the ASSURE and S-TRAC studies, was poor. Furthermore, as was highlighted in a recent study, even when broken down by quartiles of different dose intensities, there was no difference in DFS in the ASSURE trial[5]. Despite these underwhelming initial trial results, we are awaiting reporting of three ongoing trials: (i) ATLAS – axitinib vs placebo among patients with ≥T2 or N+ disease with >50% clear cell histology; (ii) SORCE – sorafenib (1 vs 3 years) vs placebo among patients with Leibovich stage 3-11 disease with both clear and non-clear cell histology; and (iii) EVEREST – everolimus vs placebo among patients with T1b-4 or N+ disease with both clear and non-clear cell histology.

The concept of RCC histology is important. S-TRAC enrolled only patients with clear cell RCC, which Dr. Heng suggests may partially explain the DFS improvement and may be a necessary strategy to enrich for patients that benefit from therapy. However, as he cautions, limiting enrollment to clear cell histology marginalized papillary and other histologies.

The concept of the Recurrence Score was previously developed by Dr. Bernard Escudier's group and published in 2015[6]. This was developed retrospectively for patients with localized clear cell RCC stages I-III, using gene expression assay using tumor FFPE. The developmental cohort was performed at the Cleveland Clinic and subsequently validated in the French cohort, followed by comparison against the Leibovich Score. In this study, the Leibovich Score had a c-index for predicting recurrence of 0.74, the 16-gene Recurrence score gene assay c-index was 0.79, and the Leibovitch + 16 gene assay Recurrence score together had a c-index was 0.81. However, as Dr. Heng notes, the recurrence scores are only helpful if there is appropriate adjuvant therapy, which to date is marginal. With Dr. Escuider's presentation[2], the 16-gene recurrence score is now externally validated, raising a number of considerations: (i) these are subgroup analysis, not prospective randomization by stratification, (ii) only 34% of S-TRAC patients were included in the analysis since not everyone had tissue available, (iii) we need to determine additional information the Recurrence Score provides beyond other criteria (ie. Leibovich) which already exist, and (iv) there was not enough power to detect significant interaction between Recurrence Score and sunitinib, suggesting there could be effect modification not detectable due to the small sample size. Prospective studies assessing Recurrence Score, particularly with PD1 trials should be strongly considered.

Dr. Heng concluded by stating once again that adjuvant pazopanib should not be used. The 16-gene Recurrence Score is now externally validated, but should not be used solely for now to determine if patients will benefit from adjuvant sunitinib, since it is not predictive. The optimal adjuvant patient is still controversial however we have hints based on subgroup analysis that these patients are likely clear cell histology, receive higher dose medication, higher stage, and higher Recurrence Score. Patient participation and tissue collection is critical in advancing predictive biomarkers for adjuvant therapy.

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AUA 2017 // MAY 12-16, 2017 // BOSTON, MA

The American Urological Association's annual meeting assembled thought leaders from around the world to provide the very latest advancements in urologic medicine. The AUA's mission is being at the forefront of developing innovative, evidence-based urologic education for urologists and urologic health care professionals worldwide. In this issue's Spotlight, we feature selected commentaries written by urologic oncology fellows and physicians from top institutes across the nation in Prostate, Kidney and Bladder Cancer.

We welcome you to read additional conference coverage from the AUA 2017 conference and other conferences at: www.urotoday.com/conference-highlights


Ramon Guiteras Lecture:
Why the Y Chromosome?
Presenter: David Page, MD
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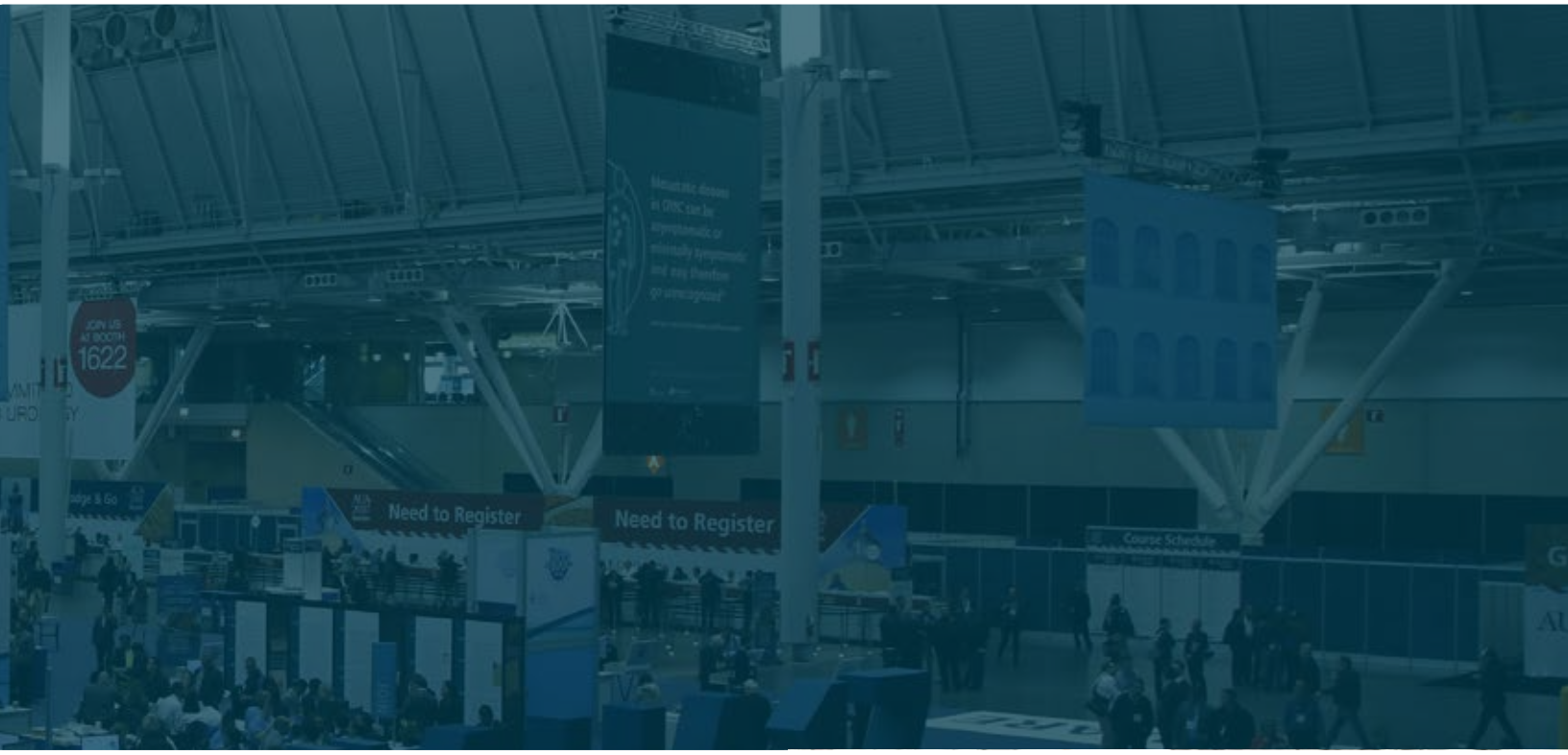
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Prostate Cancer

American Urological Association (AUA) 2017: Best Prostate Cancer Papers from Past Years

Dr. Mark Preston provided an overview of impactful papers in prostate cancer (PC) research in 2016 at the one of the Society of Urologic Oncology sessions at the 2017 AUA Annual Meeting.

Two important papers in the PC screening arena included the New England Journal of Medicine letter re-evaluating prostate-specific-antigen (PSA) testing rates in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial or PLCO trial, and the Genome-wide Association Study PSA single nucleotide polymorphisms (SNPs) manuscript. The PLCO 2009 PSA screening trial noted no improvement in survival with PSA screening, but there was a reported 50% contamination rate (men in the control arm receiving PSA screening). This letter delved into rates of testing during the trial, which was administered as a questionnaire to a subgroup of control patients, demonstrating that, in fact, more than 80% of controls without baseline screening received a PSA test during the trial. The letter was important since it likely contributed to the revised Grade C recommendation among men 55 to 69 years of age. The Genome-wide Association Study trial identified 40 genome-wide significant SNPs, 19 of them being novel entities. These 40 SNPs explained 9.5% of PSA variations in non-Hispanic whites, since more than 50% are PSA-associated, independent of PC.

The PROMIS Study was highlighted as an important paper for PC diagnosis in 2016, assessing whether multiparametric magnetic resonance imaging (mpMRI) used as a triage test may allow men to avoid an unnecessary transrectal ultrasound-guided prostate biopsy and improve diagnostic accuracy. In this multicenter study, 576 men with a PSA of less than 15 ng/mL underwent an mpMRI followed by a transperineal mapping biopsy. The study found that for significant cancer, mpMRI was more sensitive (93%) compared with transrectal ultrasound-guided prostate biopsy (48%), but less specific (41% vs. 96%). Using mpMRI to triage men may allow 27% of patients to avoid a primary biopsy and diagnose 5% fewer clinically insignificant PC.

The much acclaimed and highly publicized ProtecT Trial was highlighted as an important paper in the category of initial treatment for PC. In this trial, 1643 men with newly diagnosed PC agreed to undergo randomization to either active monitoring, surgery, or radiotherapy. The primary outcome of PC mortality was not reached as only 17 (1%) patients died of PC. The monitoring group was more likely to have progression or develop metastatic disease, and there was no significant difference between radiation and surgical treatment. The main emphasis of this trial was that the natural history of PC is very long and places importance on assessing each patient's life expectancy. Also, the Australian randomized, controlled trial subjecting 326 men to open versus robotic radical prostatectomy was published in 2016. The trial's major findings were that there was no difference in urinary or sexual function at three months' follow-up and no difference in positive marign rate (10% open, 15% robotic). As Dr. Preston mentioned, this showed that surgical randomized, controlled trials are feasible and should be performed. The ASCENDE-RT was a randomized trial comparing two methods of dose escalation for intermediate- and high-risk PCa, with all participants receiving 12 months of androgen deprivation therapy (ADT). After 8 months of ADT, all men received 46-Gy of pelvic external-beam radiation therapy (XRT) followed by a 32-Gy XRT boost, and then randomization to receive a brachytherapy boost 3 weeks after XRT. Compared with men receiving only XRT, those randomized to brachytherapy boost were twice as likely to be free of biochemical recurrence at 6.5 years' follow-up.

Several trials in the setting of locally recurrent PCa were highlighted. A double-blind, placebo-controlled trial involving 760 men who underwent prostatectomy with a pT2 or pT3, N0 with a PSA of 0.2 to 4.0 ng/mL set to undergo radiation therapy were randomized to either 24 months of bicalutamide or placebo. The trial found that the addition of bicalutamide to salvage XRT resulted in significantly higher overall survival rates: 12 year—bicalutamide 76.3% versus placebo 71.3% (hazard ratio 0.77, P = .04). A subsequent GETUG multicenter RCT was designed to establish the effect of adding short-term ADT at the time of salvage XRT on biochemical outcome and overall survival among men with rising PSA. There were 743 men who were randomized to salvage XRT or salvage XRT plus short-term goserelin. The results showed that XRT + goserelin resulted in improved 5-year PFS (80% vs. 62%, hazard ratio 0.50, P = <.001).

The final paper, in the metastatic setting, highlighted the frequency of inherited mutations in DNA-repair genes (ie, BRCA2) in patients with metastatic PCa. Among 692 men, 20 DNA repair genes were assessed; 11.8% of individuals with metastatic disease had inherited DNA-repair gene mutations, which were significantly higher than in those with localized PCa. The implications of these findings are that they will allow us to identify men who may have sustained responses to poly (ADP-ribose) polymerase or PARP inhibitors and platinum-based chemotherapy.

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Genetic Testing in Inherited Prostate Cancer Risk: Consensus Statement

Dr. Veda Giri provided a high-level talk regarding the latest consensus statement on genetic testing for prostate cancer (PC) risk at the Society of Urologic Oncology 2017 American Urological Association's Annual Meeting.

Dr. Giri elegantly delineated why we need a consensus statement this year, noting the recent studies linking BRCA2 mutation to aggressive PCa and the higher rates of PCa in families with Lynch syndrome as well as the Genome-wide Association Study identifying multiple common variants in prostate-specific-antigen (PSA) risk. PC-multigene panels have certainly focused on BRCA1/2 mutations, and Dr. Giri observed that these specific mutations are now mentioned in the most recent National Comprehensive Cancer Network

guidelines. But the questions remain: how do we manage, screen, and test these patients? She indicated that the framework of the consensus statement for genetic evaluation of inherited PC is broken down to referral criteria, genetic counseling, genetic testing, and management.

The criteria for referral for genetic counseling (with excellent consensus agreement) included patients who either have (i) first-degree relatives diagnosed with PC who are 55 years of age or younger, or have a personal diagnosis of PC at age 55 years or younger with a first-degree relative diagnosed with PC at any age or death due to PC in a first-degree relative at 60 years of age or younger; or (ii) two close blood relatives with PC on the same side of the family, with at least one diagnosed at age 55 or younger; or (iii) any first-degree relative with cancer in a hereditary situation (ie, Lynch syndrome) who is diagnosed with PC at 50 years of age or younger; or (iv) tumor sequencing that shows mutations in hereditary cancer genes.

The criteria that should be considered for genetic testing for inherited PC (moderated to excellent consensus agreement) include those with PC who have (i) families with syndromes consistent with hereditary breast, ovarian, or PC or Lynch syndrome; or (ii) men with two or more close blood relatives on the same familial side; or (iii) every man with metastatic castration-resistant PC (67% consensus agreement). Recommendations specific to which genes should be tested included expanding genetic testing to encompass hereditary cancer syndromes (ie, BRCA1/2, HOXB13) or a broader family cancer history and to provide context of relevance of genes based on a family history of disease aggressiveness.

For those who have mutations, the panel developed consensus statements targeting how to screen these patients. For men with a BRCA2 mutation, the consensus was 56% for obtaining a PSA at age 40 or 10 years prior to the youngest PC diagnosis in the family. Furthermore, the interval of screening should be yearly or determined by baseline PSA (76% consensus). For patients with HOXB13 mutation, similar recommendations are made as to men with BRCA2 mutation, which is the first such recommendations for individuals with HOXB13 mutation.

In summary, this is the initial centralized, multidisciplinary consensus to address a working framework toward addressing genetic evaluation for inherited PC. Dr. Giri concluded that "This is a dynamic field that will require updating of the guidelines in the future."

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Combination or Sequential Therapy for Castration-Resistant Prostate Cancer

Dr. Chris Sweeney concluded an excellent 'Best of Boston' session at the 2017 American Urological Association Annual Meeting by discussing a very important topic in the setting of advanced disease, namely what combination or sequential therapy should we be considering for castration-resistant prostate cancer (CRPC).

The speaker began his talk by noting that we have level-1 evidence of a single agent with overall survival benefit after another agent, namely (i) cabazitaxel after docetaxel, (ii) abiraterone after docetaxel, and (iii) enzalutamide after docetaxel. However, we must balance treatment burden against baseline symptoms and the gain from therapy/likeliness of response. The more treatments with a specific therapy a patient can receive, the more likely he has of responding. Monitoring should include scanning when a patient experiences vague symptoms/prostate-specific-antigen rise and avoid switching treatments too late.

Dr. Sweeney mentioned that deciding to use chemotherapy in men with CRPC depends on a number of factors. These include: (i) whether the patient is fit for chemotherapy, (ii) if there is a lack of alternative options with lower treatment burden on a case-by-case basis, and (iii) whether radium-223 with a lower treatment burden is a viable alternative. Docetaxel and cabazitaxel have an adverse-event profile that precludes them from being viable treatment options for all patients, particularly because they are more commonly of older age.

Given the high mutational load associated with CRPC, not everyone is a candidate for androgen-receptor (AR)-targeted therapies. Furthermore, the mutation load may increase over time, as Dr. Sweeney noted that when enzalutamide was given prior to docetaxel, there was an 89% decrease in risk of radiographic progression, but only 60% when given after docetaxel. This implicates the ARv7 mutation and according to Dr. Sweeney, even in the absence of a clinical assay, we can rely on clinical features, namely prior use of abiraterone or enzalutamide (ARv7 is more common in the second line), and an anaplastic variant to 'assess' ARv7 status.

Dr. Sweeney concluded that he believes "we will have data showing combinations are more effective than sequential single agents," especially for high disease burden multiclonal CRPC. He also noted that "we will have biomarkers to guide which agents to combine and newer ones (magnetic resonance imaging/positron emission tomography) will tell us when to switch," but for now we should rely on symptomatology, current imaging, and PSA. We eagerly await the results of pilot and ongoing trials that are assessing combinatorial therapies.

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Prostate Cancer

Journal of Urology 2016 Top Papers—Prostate and Testis Cancer

In this session, Dr. Laurence Klotz covered the highlights of prostate and testis cancer from the Journal of Urology during 2016 and early 2017. There were 290 total manuscripts on prostate cancer (PC) and 16 on testis cancer.

Stasivam and colleagues (J Urol. 2016;195:74-79) looked at 392 men on active surveillance (AS) with Gleason sum 6. The question was asked as to whether magnetic resonance imaging (MRI) can be used to avoid confirmatory biopsy. A decision model incorporating prostate-specific-antigen density, percentage of positive cores, MRI findings, and extent of cancer in the biopsy core was developed. Using this model, 76% of biopsies could be avoided if one accepts missing 2.3% of high-grade cancers. Using a more stringent "miss rate" of 1%, one can avoid 52.6% of biopsies.

O'Neil et al. (J Urol. 2016;195:321-329) considered differences in functional outcomes between patients undergoing open versus robotic prostatectomy. This retrospective review considered 1505 open and 933 robotic procedures. At 6 months, both urinary and erectile functions favored the robotic approach. While the difference in erectile function persisted at 12 months, there was no variation in continence at 12 months.

Phillips and associates looked at differences in adverse events for intermittent versus continuous androgen deprivation therapy in 9772 patients with metastatic PC. This population-based study found a lower risk for adverse events in the intermittent androgen deprivation therapy group. Specifically, there was a lower risk of serious cardiovascular events (hazard ratio [HR] 0.64), heart failure (HR 0.62), and fracture (HR 0.52).

Moore and colleagues (J Urol. 2017;197:1006-1013) considered the effect of dutasteride on MRI-visible PCas with a total of 42 men included in the analysis. The authors observed a 36% reduction in size of PCs in patients on dutasteride versus a 12% increase in those on placebo. The oncologic ramifications of this finding require further elucidation.

Rosenkrantz et al. (J Urol. 2016;196:1613-1618) provided a consensus statement on the use of MRI in patients with prior negative prostate biopsy. Prostate Imaging—Reporting and Data System or PI—RADS 3-5 lesions warrant repeat targeted biopsy. Cognitive fusion remains a reasonable approach in skilled hands. At least 2 targeted cores should be obtained. Systematic concurrent sampling should be determined on a case-specific basis. Other ancillary markers may be of value in identifying patients who warrant re-biopsy. Finally, measuring quality is critical to ensure that optimal results are obtained.

Truong and associates offered an interesting observation (J Urol. 2017 Feb 3) in a small series of men with initial negative biopsy who had a targeted biopsy on MRI followed by radical prostatectomy. Namely, a cribriform pattern on the radical prostatectomy specimen was not readily observed as a lesion on MRI. The authors suggested that this may be responsible for a portion of the negative outcomes in contemporary primary Gleason pattern 4 disease.

Thorstenson and colleagues (J Urol. 2017;197:61-66) performed a population-based study comparing survival outcomes in younger men (919 aged 35-49 years) with older men (45,098 aged 50-66 years). Stage for stage, young men were found to have worse survival outcomes relative to older men.

Muthigi et al. (J Urol. 2016;197:327-334) considered what causes us to "miss the mark" during MRI-targeted biopsies. Mechanisms for undergrading included reader oversight, error in technique, and intralesional heterogeneity.

Dr. Klotz highlighted a study performed in Toronto, Ontario, Canada, using his AS cohort. Musunuru and colleagues (J Urol. 2016;196:1651-1658) demonstrated that patients with secondary and primary Gleason pattern 4 PCa on AS have worse outcomes relative to those with Gleason 3+3=6 tumors.

The final PCa manuscript considered was related to focal therapy. Eggener and associates (J Urol. 2016;196:1670-1675) looked at MRI-guided focal laser ablation of PC and showed some promising short-term results. At 1 year, most individuals had a negative biopsy. The needs to define optimal patient populations and to acquire longer-term results may well prevent widespread adoption of this burgeoning technology.

Two papers on testis cancer were highlighted. Wymer and colleagues (J Urol. 2016;197:684-689) compared survival outcomes for patients managed according to National Comprehensive Cancer Network guidelines versus those who were not managed based on best-practice statements. Patients not managed by guideline statements have worse risk for relapse (HR 2.49, 95% confidence interval 1.61-3.85) relative to those managed appropriately.

Lastly, Banerji et al. (J Urol. 2016;196:1117-1122) queried the National Cancer Data Base for sex cord stromal (Leydig/Sertoli) tumors. While these represent only 0.4% of testis cancers, they are not inconsequential. Five-year survival was 91% for Leydig cell tumors and 77% for sertoli cell tumors. The authors cautioned against assuming a benign nature for sex cord stromal tumors, suggesting that more aggressive treatment may be needed for some of these patients.

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Radical Prostatectomy Versus Observation for Early Prostate Cancer: Follow-Up Results of the Prostate Cancer Intervention Versus Observation Trial (PIVOT)

Dr. Timothy Wilt presented the updated follow-up data from the PIVOT, previously reported in 2012.[1] In brief, after 19.5 years of follow-up, an absolute risk reduction (ARR) of 5.5% (95% confidence interval [CI]; -1.5%-12.4%, P = .06) was found for all-cause mortality (61.3% vs. 66.8%) in patients treated with prostatectomy.

In addition, an ARR of 4.0% (95% CI; -0.2-8.3%, P = .06) was found for prostate cancer (PC)-specific mortality (7.4% vs. 11.4%). By comparison, the ARR for all-cause and cancer-specific mortalities in the 10-year follow-up analysis previously reported in The New England Journal of Medicine were 2.9% and 2.6%, respectively. On subgroup analysis, surgery reduced all-cause mortality among men with intermediate-risk disease (ARR = 14.5%, 95% CI 2.8%-25.6%). By contrast, no benefit was seen in the low- or high-risk groups. While surgery reduced the need for treatment of progressive disease, there were increased incidences of therapy-related long-term complications such as urinary incontinence and erectile and sexual dysfunction.

The PIVOT was the first prospective, randomized, controlled study to assess the impact of surgery in PC patients in the PSA screening era. Long-term follow-up of an earlier study in those with clinically diagnosed, localized PC demonstrated an ARR of 11% in cancer-specific survival in the surgically treated group.[2] However, with the advent of PSA screening and the ensuing stage migration, the benefit of prostatectomy in clinically low-risk PC was called into question. The original analysis of the PIVOT demonstrated a lack of benefit in patients with clinically low-risk PC. Based on this conclusion, the strategy of active surveillance has been increasingly adopted in the management of low-risk localized PC.

However, the implications of the PIVOT results for intermediate- and high-risk PC remain hotly debated.[3-6] When separated into the different D'Amico risk classifications, surgery attenuated all-cause mortality in the intermediate-risk group and cancer-specific mortality in the high-risk group.[1] Taken together, the PIVOT was interpreted by many as an affidavit for the futility of surgical treatment for PC. Even with longer follow-up, many weaknesses in the trial design deserve mention.

The PIVOT was created to demonstrate a 25% relative reduction in mortality. To put this in perspective, early coronary artery bypass graft versus medical management demonstrated a mere 17% relative reduction in overall mortality.[7] To achieve such a lofty objective, selection criteria to include patients with minimal competing risks were of paramount importance. The overall mortality rates at the 10-year analysis were 47.0% and 49.9% in the treatment and control groups, respectively. These rates were high compared with age-matched subjects in the general population (20.6%), indicating a higher incidence of comorbidities.[8] In the face of these restrictions, the enrollment in the trial fell short of the numbers needed to demonstrate statistical difference.[4] In addition to these shortfalls, the intent-to-treat analysis was marred by a 20.5% incidence of definitive treatment in the observation arm. While longer follow-up incrementally added to the strength of the analysis, many of the abovementioned deficiencies could not be rectified.

Notwithstanding the PIVOT's inadequacies, the trial remains a benchmark study, pointing to the critical importance of uncoupling treatment from diagnosis in the PSA era as well as the need for more accurate characterization of the different risk categories of disease.

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Prostate Magnetic Resonance Imaging: The Truth Lies in the Eye of the Beholder

During one uroradiology poster session at the 2017 American Urological Association Annual Meeting in Boston, MA, Dr. Joseph C. Riney and colleagues from Hershey, PA, presented their prostate magnetic resonance imaging (MRI) experience, specifically to assess the accuracy and variability of pelvic MRI interpretation among the body radiology team versus a senior faculty member. With improving technology and clinicians increasingly relying on multiparametric MRI findings for subsequent targeted biopsies and presurgical planning, evaluation of radiology interobserver agreement is important.

This study included a single-institution evaluation of 233 consecutive men diagnosed with prostate cancer who ultimately had a prostatectomy. These patients all had a presurgical pelvic 3T surface body coil MRI read by a fellowship-trained body radiologist, and subsequently a senior radiologist was selected to re-read all pelvic MRIs blinded to the initial interpretation. Specific to extraprostatic extension (EPE), there was low concordance comparing the primary versus repeat MRI interpretation (kappa = 0.22). Interestingly, when

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the senior radiologist re-read his own initial interpretation (n = 93), the kappa score for EPE was still low at 0.36. A comparison of initial MRI interpretation versus that re-read by a senior radiologist noted universal improvements in EPE parameters, including sensitivity (30.3% vs. 56.1%), specificity (80.2% vs. 88.6%), positive predictive value (PV) (37.7% vs. 66.1%), negative PV (74.4% vs. 83.6%), and accuracy (66.1% vs. 79.4%). Seminal vesicle invasion interpretation of initial MRI interpretation versus re-read yielded similar sensitivity (18.2% vs. 27.3%), specificity (97.2% vs. 93.8%), positive PV (40.0% vs. 31.6%), negative PV (91.9% vs. 92.5%), and accuracy (89.7% vs. 87.6%). The study's strength includes a single senior radiologist re-reading all prostate MRIs, whereas a limitation of the study includes a single-center, retrospective study design.

It is crucial for our radiology colleagues to evaluate their performance reading prostate MRIs, and this study is commendable for demonstrating that even at academic medical centers, interobserver agreement may be low. As we have seen from other presentations during this session, perhaps a 'consensus' radiologic interpretation (with a senior radiologist) may be more reliable and should be evaluated in future prospective studies.

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DNA Repair Defects in Prostate Cancer

Dr. Matthew Smith started 'The Best of Boston' session off at the 2017 American Urological Association's Annual Meeting by discussing DNA repair defects in prostate cancer (PC).

Dr. Smith presented a case of a 54-year-old man with metastatic castration-resistant prostate cancer (mCRPC) who was initially diagnosed in 2008 with PC and underwent a laparoscopic prostatectomy for Gleason 4+5 disease, pT3bN0 adenocarcinoma. In 2010, his prostate-specific antigen was 2.2. Staging demonstrated retroperitoneal lymphadenopathy, so continual androgen deprivation therapy was started. In 2011, he progressed to CRPC, and since then has been on sequential treatment with sipuleucel-T, abiraterone acetate with prednisone, and subsequently with docetaxel. His family history was notable for his father being diagnosed at age 62 and succumbing to PC in his early 70s, so he was then referred for a genetics evaluation, which demonstrated pathogenic germline mutation for BRCA2. As Dr. Smith observed, the BRCA2 germline mutation in PC has revealed a heritable, particularly aggressive form of PC. BRCA2 alterations lead to defective DNA repair, transcription, and cell cycle regulation. As we know, germline BRCA2 mutations have historically been associated with breast and ovarian cancer and now, more recently, with PC and pancreatic cancer.

The mutational landscape for mCRPC specifically is quite burdensome, as a recent study noted that DNA repair alterations were found in 19.3% of these patients. Clinically, this has led to the development of poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib. PARP inhibitors specifically target strands of damaged DNA and lead to cellular apoptosis, which has demonstrated burden of disease regression. However, as Dr. Smith mentioned, future clinical trials that assess PARP inhibitors for PC need to answer the questions of (i) Which PARP inhibitors should we use? (ii) In which disease states should we employ them? (iii) Which biomarker should we utilize to assess eligibility and response? (iv) Which endpoints should we be assessing? One particular phase II study in this setting that is currently ongoing is the GALAHAD, a multicenter study for men with mCRPC and DNA repair anomalies.

Dr. Smith summarized his talk by noting that pathogenic germline mutations in DNA repair genes, as well as acquired DNA repair defects, are relatively common in metastatic PC. Preliminary evidence suggests that PARP inhibitors are active in treatment of refractory mCRPC. Dr. Smith's recommendations were that patients should be considered for genetic counseling and testing if they are metastatic and/or have high-grade PC. Furthermore, individuals with treatment-refractory mCRPC should be considered for tumor genetic analyses and encouraged to participate in clinical trials.

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The ERSPC Versus the ProtecT Study: Outcomes After Active Surveillance Compared to Surgery and Radiotherapy for Localized Prostate Cancer

The long-term safety of active surveillance (AS) remains a controversial topic of debate. The ProtecT Study published 10-year outcomes after randomization to active monitoring (AM), radiotherapy (RT), or radical prostatectomy (RP); with higher-risk patients and a less strict follow-up protocol than contemporary AS. In the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam, a subgroup of patients also received AM/AS, although it was utilized according to a more strict protocol (eg, Prostate Cancer Research International Active Surveillance or PRIAS).

Dr. Frank-Jan Drost presented a study evaluating death rates among men with low- to intermediate-risk prostate cancer (PC) treated with AS, RT, or RP in the ERSPC and compared these with ProtecT patients. Men with low-risk (Gleason score [GS] 6, cT1C/cT2A) and intermediate-risk (GS ≤3+4, cT1c/cT2) PC, diagnosed in the first and second screening rounds of the ERSPC study (1993-2003) were included. Multivariate Cox proportional hazard analyses were

performed, controlling for age, prostate-specific antigen, clinical stage, GS, and comorbidities.

Of the 2280 PC patients from the ERSPC who were analyzed, 905 and 1275 had low- and intermediate-risk PC, respectively. Median age and prostate-specific antigen in the low- and intermediate-risk PC were 66.4 years and 4.3 ng/mL; 66.6 years and 4.5 ng/mL, respectively. Median follow-up was 13 years. In the low-risk group, the hazard ratio (HR) for PC-specific death for RT/RP (n = 370/312) versus AS (n = 223) was 0.61 (95% confidence interval [CI] 0.18-2.0, P = .41). The HR for overall death was 1.29 (95% CI 0.97-1.72). In the intermediate-risk group, the HR for PC-specific death for RT/RP (n = 501/526) versus AS (n = 248) was 0.65 (95% CI 0.25-1.64, P = .36). The HR for overall death was 1.23 (95% CI 0.95-1.59).

In the ProtecT study, the HR for PC-specific death for RT versus AM was 0.51 (95% CI 0.15-1.69) and for RP versus AM 0.63 (95% CI 0.21-1.93), P = .48. The specific HR for overall death was not specified (P = .87 across treatment groups).

In summary, the HR for PC-specific death for AS versus immediate active therapy between the ERSPC Rotterdam and ProtecT appear to be quite similar. Although the ERSPC was not randomized but did include 13 years of complete follow-up, these data confirm that initial therapy with AS, when compared with immediate active therapy, results in similar low PC-specific death rates.

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Combining 4KScore and Magnetic Resonance Imaging (MRI) for Prostate Biopsy Decision Making

At the prostate cancer (PC) diagnosis and screening podium session during the 2017 American Urological Association's Annual Meeting, Dr. Karim Marzouk and his colleagues presented their work from the Memorial Sloan Kettering Cancer Center assessing the utility of multiparametric MRI (mpMRI) as a follow-up test to the 4Kscore. As the recently published PROMIS MRI trial demonstrated, 11% of men with a normal MRI will have high-grade disease.[1] Since we have many biomarkers that include imaging modalities available to clinicians in the prebiopsy setting, studies delineating appropriate patient-specific sequences of tests are important.

In this study, the 4Kscore results from the United States prospective validation study were combined with mpMRI data available from the PROMIS study. The co-authors used likelihood ratios for MRI that detected high-grade disease from PROMIS (positive and negative likelihood ratio of 1.58 and 0.17, respectively) and applied these ratios to probabilities of 4Kscores. Four unique populations were identified based on a threshold for biopsy of 7.5% risk of high-grade disease: (i) men with a very low 4Kscore for whom risk would not be less than 7.5%, even with positive MRI, (ii) men with 4Kscores of less than 7.5% whose risk would be 7.5% or more if the MRI was positive, (iii) men with 4Kscores of 7.5% or higher whose risk would be less than 7.5% if the MRI was negative, and (iv) men with high 4Kscores whose risk would remain 7.5% or greater, even if MRI was negative. In the 4Kscore validation study, 1012 men underwent prostate biopsy, with 23% being diagnosed with Gleason 7 or higher disease. The range of 4Kscores that could be influenced by the results of MRI included 26% of the population with a risk of less than 5% (group 1), 10% with a risk of 5.0%-7.4% (group 2), 45% with a risk of 7.5%-32% (group 3), and 21% with a risk of more than 32% (group 4). Importantly, the net benefit of using 4Kscores alone was 17.7%, mpMRI of 17.6%, and combined strategies of 18.2%.

In summary, this is an sophisticated study combining imaging and biomarkers to further delineate who should or should not undergo a biopsy. Using mpMRI in the setting of low-to-intermediate 4Kscores results in a biopsy strategy with a higher net benefit compared to using either modality alone.

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Bladder Cancer

Journal of Urology 2016: Top Papers: Bladder and Renal Cancer

Dr. Badrinath Konety presented the most influential bladder and renal cancer papers published in the Journal of Urology in 2016. There were 63 high-quality papers in these areas in the Journal last year, of which he highlighted approximately 10%.

In kidney cancer, some of the most interesting and novel research is being done with regard to the effect of sarcopenia (decreased muscle mass) on oncologic and postsurgical outcomes. Using computed tomography-guided measurements of sarcopenia, Psutka et al. published their data from the Mayo Clinic showing that sarcopenic patients have worse long-term survival following surgery than those who are nonsarcopenic. This includes those who are obese but have radiographic evidence of sarcopenia. Fukushima et al. published a parallel paper demonstrating similar survival effects of sarcopenia on individuals with metastatic renal cell carcinoma. More data in this field are sure to come, and they promise to be useful clinical tools for interventions and management of these patients in the future.

Azawi et al. published their series on patients undergoing same-day-surgery laparoscopic nephrectomies. The researchers prospectively operated on a highly selected cohort of individuals who were at low risk for complications. They were able to discharge 92% of them within 6 hours postoperatively, with another 6% discharged within 24 hours. There were few major complications. They standardized the treatment algorithm: transperitoneal laparoscopy, preoperative administration of gabapentin, paracetamol, and ibuprofen, minimizing postoperative narcotic intake, and utilizing the surgeon as the case manager. The key to success in this setting is appropriate patient selection and the use of evidence-based enhanced recovery after surgery (ERAS) pathways that are shown to improve postoperative outcomes. Understandably, it may be difficult for most urologists to jump on this bandwagon right now, but the proof of concept is important.

In bladder cancer (BC), there were multiple important contributions to the literature in 2016. Park et al. published their findings targeting delays in receiving radical cystectomy (RC) after initial diagnosis. Prior work had demonstrated that delays of more than 12 weeks from transurethral resection of bladder tumors (TURBTs) to RC may portend worse survival. In this study, patients were administered neoadjuvant chemotherapy, and the time to RC was measured along multiple time points (diagnosis to TURBT, TURBT to chemotherapy, chemotherapy to RC). They found there were significant delays to RC (>20 weeks), but that this did not impact survival. Therefore, they concluded that neoadjuvant chemotherapy is still appropriate, even if it delays time to RC. This is welcome news for most healthcare practitioners who have made the shift to giving neoadjuvant chemotherapy prior to RC.

Albissini et al. evaluated disease recurrence in a large cohort of patients undergoing minimally invasive RC. Some 8.7% of patients recurred in fewer than 24 months, and the patterns of recurrence were quite varied. Compared with a standard RC, they concluded that their data suggest an increased risk of early recurrence following minimally invasive RC. They proposed multiple potential reasons for this finding, such as the use of pulsatile pneumoperitoneum or decreased systemic pH from absorbed CO2. Realistically, as more patients undergo minimally invasive RC, we will have more data to delineate whether this increased risk is real. Of course, urologic oncologists will be paying very close attention to this space.

Smith et al. published a fascinating bird's-eye-view of BC mortality trends in the United States starting in the mid-20th Century. They looked at historic time periods and geographic distributions of BC mortality and identified risks associated with higher frequencies of BC. Risks included some well-known factors such as smoking and well-water use. However, air pollution, unemployment, and lack of insurance were also risk factors—a point that is particularly poignant given the current political discourse regarding environmental and health insurance policies.

Sharma et al. published a highly cited paper showing that preoperative patient-reported mental health is associated with postoperative high-grade complications following RC. Poorer patient-reported mental health portends worse complication rates. The effect of psychological states on perioperative outcomes is virtually unknown, and it will be exciting to see where this research leads in the future.

Finally, Anderson et al. published the Memorial Sloan Kettering Cancer Center-developed and validated checklist for surgeons performing transurethral resection of bladder tumors (TURBT. The aim was to standardize biopsy technique, reporting, and measurement parameters to improve the quality of this extremely common procedure. This is a colossal step in the right direction for improving the quality and efficacy of such a common urologic procedure and, hopefully, it will gain widespread acceptance.

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WRITTEN BY: SHREYAS JOSHI, MD, FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Muscle-Invasive Bladder Cancer Guidelines

Jeffrey Holzbeierlein, University of Kansas, discussed the Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer (MIBC) guidelines. The American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) have formulated an evidence-based guideline for the management of MIBC.

The guideline offers recommendations on the diagnosis, management, and surveillance for patients with MIBC. Those with variant histology present an ominous diagnosis and may require a divergence from the standards below. Aside from obtaining a full history and performing a physical examination as well as transurethral resection of bladder tumor (TURBT), the panel strongly recommended an examination under anesthesia at the time of TURBT.

They also suggested cross-sectional imaging without specific recommendations. However, the panel did not recommend positron emission tomography-computed tomography (CT) over conventional CT or magnetic resonance imaging. Chest imaging is recommended for all patients, but a CT thorax scan is also suggested for individuals with a smoking history. Curative treatment options should be discussed before determining a plan of therapy that is based on both patient comorbidity and tumor characteristics, including surgery, chemotherapy, and radiotherapy. Multidisciplinary consultation and discussion are strongly encouraged.

The panel strongly recommends use of neoadjuvant chemotherapy with the focus on use of cisplatin-based chemotherapy. Radical cystectomy (RC) with bilateral pelvic lymph node dissection (internal iliac, external iliac, and obturator lymph nodes resected at minimum) should be performed as soon as possible within a recommend 12 weeks of diagnosis. In patients undergoing RC, all diversions, including ileal conduit, continent cutaneous, and orthotopic neobladder, should be discussed. Those who did not receive neoadjuvant chemotherapy should be offered adjuvant cisplatin-based chemotherapy when advanced disease present on pathology. Perioperative thromboembolic prophylaxis is recommended as well as clinical care pathways that may lessen ileus, including the use of mu-opioid-antagonist therapy.

For patients who desire to retain their bladder, and for those with significant comorbidities for whom RC is not a treatment option, bladder preservation options may be considered. Maximal debulking TURBT and assessment of multifocal disease/carcinoma in situ should be performed. Patients with MIBC who are medically fit and consent to RC should not undergo partial cystectomy or maximal TURBT as primary treatment. Radiotherapy should be administered with chemotherapy and subsequent surveillance, including cystoscopy and imaging (see below).

Surveillance for all patients should include imaging for 6 to 12 months for 2 to 3 years, repeated annually along with laboratory work at 3 to 6 month intervals for 2 to 3 years, then annually thereafter. Those with retained urethras should be monitored for urethral recurrence. Patient survivorship is strongly encouraged. In summary, the MIBC guidelines are comprehensive and mirror the European Association of Urology guidelines. However, the support from numerous organizations demonstrates the multidisciplinary approach needed to manage this lethal disease.

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The Benefit of Continuous Saline Bladder Irrigation After Transurethral Resection in High-Grade Non-Muscle-Invasive Bladder Cancer: A Single-Center, Randomized, Prospective Study

Takehisa Onishi, Ise Red Cross Hospital, Ise, Japan, presented a randomized trial comparing patients with high-grade non-muscle invasive bladder cancer (NMIBC) who received continuous saline bladder irrigation (CSBI) to those who received a single postoperative intravesical administration of mitomycin C (MMC). The authors aimed at evaluating the efficacy and safety of CSBI in patients with high-grade NMIBC.

A total of 236 patients were randomized. After exclusion, however, 76 and 74 patients were randomized to CSBI versus MMC, respectively. The primary endpoint was recurrence-free survival. Secondary endpoints were progression-free survival and adverse events. All patients underwent similar surveillance, with none of them receiving further treatments until first recurrence was noted.

There was no significant difference in recurrence-free survival. Moreover, there was no difference in progression-free survival. There was significantly decreased adverse events noted in the CSBI versus MMC group (8% vs. 38%, $P < .001$), respectively. The authors concluded that CSBI was not inferior to MMC and may be a safe and less costly alternative in patients with high-grade NMIBC.

The findings must now be interpreted in the context of the study design. First, the duration of CSBI required patients to be admitted overnight, which carries significant costs considering many patients often undergo TURBT as an outpatient procedure. The authors indicated that the hospital stay was the same for both groups. Second, the MMC used in this trial was 30 mg whereas 40 mg is guideline-recommended. Third, current American Urological Association and European Association of Urology guidelines do not suggest MMC in patients with intermediate-to-high-risk NMIBC. Thus, the present findings may not be applicable.

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What Is the Best Systemic Therapy for Metastatic/Invasive Bladder Cancer?

Drs. Gopa Iyer and Arjun Balar debated the relative risk/benefit profiles of cisplatin-based neoadjuvant chemotherapy versus immunotherapy.

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Dr. Iyer observed that cisplatin-based regimens are still the gold standard despite recent excitement about immunotherapy. Gemcitabine/cisplatin or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin are National Comprehensive Cancer Network category 1 recommendations for metastatic urothelial carcinoma. He stated that based on the survival curves from some trials, approximately 12% to 15% of metastatic cancer can be cured and also indicated that carboplatinum may be substituted in cisplatin-ineligible patients with overall response rates (ORRs) of 30% to 41% in select patients. However, in the second-line setting, the ORRs for this therapy drop to 10% to 20%.

For cisplatin-based neoadjuvant chemotherapy for muscle invasive bladder cancer, Dr. Iyer reminded the audience that level-1 evidence shows the benefit of this approach without worsening of surgical morbidity or delays. Southwest Oncology Group 8710 (Grossman et al.) showed improved 5-year survival of 57% versus 43% in the non-neoadjuvant chemotherapy arm. Pathologic response rate (pT0 at cystectomy) correlated strongly with long-term survival. Meta-analysis has shown 5% absolute overall survival benefit. New studies show that defective DNA damage responsive genes have exquisite cisplatin sensitivity and may be useful clinical markers for cisplatin recipients.

Dr. Balar referred to immunotherapy as "A new standard in bladder cancer." The efficacy of immunotherapy in bladder cancer makes intuitive sense given its known high somatic mutational burden, likely tobacco-carcinogen-related, leading to high levels of neoantigens. He pointed out that in some series, 50% to 70% of patients are cisplatin-ineligible and 20% to 40% are never treated (presumably over fear of adverse effects [AEs]), uncovering a huge unmet need for better tolerated but still effective therapies. Generally, immunotherapy trials in bladder cancer have shown ORRs around 15% to 20%, with median overall survival of 7 to 8 months in second line. Finally, in terms of tolerability, these agents are being given in the trial setting to much older sicker patients, suggesting fewer AEs than with traditional chemotherapy. However, there are still 15% Grade 3 or higher AEs, and immune-related AEs can be severe and must be monitored.

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WRITTEN BY: JED FERGUSON, MD, PHD, AND ASHISH KAMAT, MD, MD ANDERSON CANCER CENTER, DEPARTMENT OF UROLOGY, HOUSTON, TX

Effect of Radical Cystectomy and Urinary Diversion for Bladder Cancer Treatment on Renal Function over Time

Dr. Shahab Bozorgmehri analyzing the effect of radical cystectomy (RC) and urinary diversion (UD) for bladder cancer on renal function over time compared with a control group.

Overall, 384 patients with bladder cancer who sought care in a tertiary health care center from 2000 to 2014 were included in the study cohort. Out of these individuals, 172 had undergone RC and UD, while 212 were treated without undergoing RC and UD. Two factors were used to assess renal function decline: (a) annualized estimated glomerular filtration rate (eGFR) decline and (b) time to decrease in eGFR of 30% or more from baseline. Propensity score regression adjustment was used to address confounding by indication. Unadjusted and adjusted linear Cox proportional hazards models were used to assess the association between RC and UD, eGFR slope, and time to decrease in eGFR of 30% or more, respectively.

Mean age was 68 ± 12 years; average follow-up was 17 ± 13 months. Patients with RC and UD experienced a faster decline in renal function over time when compared with those without RC and UD. Using Cox multivariable regression models to adjust for age, propensity score, and other confounding variables, the difference in mean eGFR slope in patients with RC and UD compared with those without RC and UD, was stable and remained statistically significant ($P < .001$). Patients with RC and UD had a higher risk of eGFR decline of 30% or more compared with those without RC and UD (unadjusted hazard ratio = 1.88, 95% confidence interval: 1.35-2.63; $P < .001$); this persisted despite adjustment for age but was attenuated and no longer statistically significant after adjustment for propensity score and confounding variables (adjusted hazard ratio = 1.01, 95% confidence interval: 0.62-1.63; $P = .976$).

In conclusion, RC and UD were independently associated with a faster decline in renal function over time and also linked with a higher risk of eGFR decline of 30% or more only in the unadjusted analysis. These results add to the growing body of knowledge on the relationship between renal function decline and RC, thereby helping to formulate intervention strategies to prevent renal function deterioration in this population.

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The Whitmore Lecture

Dr. Colin Dinney delivered the always anticipated Whitmore Lecture at the Society of Urologic Oncology session at the 2017 American Urological Association's annual meeting. Dr. Dinney is a pioneer in the basic science research arena, particularly with respect to bladder cancer (BC), and most deserving of this honor.

Dr. Dinney was born in Canada and did his undergraduate and medical schoolwork at the University of Manitoba in the frozen tundra of Winnipeg. From there, he moved to Halifax, Nova Scotia, where he took his residency at Dalhousie University before moving to Houston, TX, for a fellowship in immunotherapy of renal cell carcinoma in 1989.

He never left the warmer climate of the south and has been on faculty at Houston's MD Anderson since 1992, and its chairman since 2007. Shortly thereafter, he changed the focus of his research to BC, using small institutional grants to develop orthotopic models of human BC to study metastasis and develop novel therapeutics. Early findings included identifying a reversible epithelial-mesenchymal transition during BC metastasis as well as early work assessing angiogenesis and metastasis. This further developed to identify interferon-beta gene therapy in inhibiting tumorigenicity and metastasis of BC, and anti-epidermal growth factor receptor antibodies for hindering bladder tumor growth.

To begin transitioning these early laboratory findings to the clinic, Dr. Dinney started the first SPORE program, surrounding himself with leaders in the field, including Drs. Bart Grossman and David McConkey. The first funded SPORE was in 2001, leading to five BC-specific projects. As Dr. Dinney noted, much of the success of the SPORE he has overseen has been secondary to his collaborators, including the many fellows he has had a part in training. Some of these projects include (i) characterizing the aggressive micropapillary variant of BC, (ii) development of the cytokine nomogram for predicting Bacillus Calmette-Guerin sensitivity, (iii) identifying Ral as a therapeutic target, and (iv) developing interferon gene therapy. Dr. Dinney's other accomplishments include being fellowship director from 1997 to 2005 and serving as the founding president of the Society of Urological Oncology Clinical Trials Consortium.

Dr. Dinney left the audience with a number of excellent lessons he has learned over the years: (i) you need a man, a plan (vision), and a fan; (ii) don't get married to your hypothesis; (iii) find ways to bring out the best in those around you; (iv) ask for advice but make your own decisions; (v) take responsibility for the failures but give credit for the successes; (vi) when things get tough, always take the high road; (vii) if you have to make enemies, make sure they are at home, and (viii) it does not matter where you came from but only where you are going.

As he concluded, "The road to success is paved with failure, but enjoy life when you get the opportunity."

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Isolated Red Patches Seen during Endoscopic Surveillance of Bladder Cancer—How Often Should We Biopsy?

According to Gurminder S. Mann, red patches in the bladder that are seen with cystoscopy, especially after administration of Bacillus Calmette-Guerin (BCG) in bladder cancer (BC) patients, are quite common. Distinguishing these BCG artifacts from malignancy and especially carcinoma in situ, in the absence of narrow-band imaging or photodynamic diagnostics, is difficult. There are insufficient data regarding the course of these patches and whether they remain benign over time, even if a past biopsy demonstrated no signs of malignancy.

He presented his study assessing the importance of these red patches during BC surveillance and tried to analyze how often they should be biopsied. For this study, 4805 flexible cystoscopy (FC) reports over a 12- month period (January - December 2015) were retrospectively reviewed at a United Kingdom tertiary teaching hospital. Only those undergoing cystoscopic surveillance for BC and found to have solitary red patches at FC were included in the study. Out of all the FC, 241 were performed on 183 patients as part of a surveillance protocol for BC and found to have red patches. A total of 120 individuals who experienced FC (49.8%) had a history of intravesical BCG therapy. Only 85 patients (35.3%) underwent biopsy of the demonstrated red patches. Malignancy was found in 20 of 85 biopsies (23.5%), of which 11 of 20 (55%) were carcinoma in situ. In addition, 16 of 20 of these recurrences had been biopsied previously, of which 11 (68.8%) were benign at last biopsy. Almost 70% of recurrences were found in patients who had been biopsied within the last 12 months. Importantly, no cases of malignancy were identified in those with low-risk BC.

Dr. Mann concluded by recommending a biopsy of all red patches found during endoscopic surveillance of patients with at least an intermediate-to-high-risk BC. It was also emphasized that a biopsy must be performed, especially if no previous biopsy was done within the last 12 months and independently of previous biopsy histology.

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Blue-Light Cystoscopy for Diagnosis of Urothelial Bladder Cancer: Results from a Prospective Multicenter Registry

Data exists regarding blue-light cystoscopy (BLC) using hexaminolevulinate (Cysview) to improve the detection of non-muscle invasive bladder cancer (NMIBC). Dr. Soroush T. Bazargani reported on the experience from the multicenter prospective BLC study with Cysview Registry and its utility in different scenarios. This study prospectively enrolled consecutive patients undergoing transurethral resection of bladder lesions into the registry at nine different centers and took place between April 2014 and October 2016. Exclusion criteria included those refusing catheter insertion, patients with pure upper tract or prostatic urethral lesions, and individuals who were lost to follow-up.

Overall, 1325 separate lesions were identified from 517 BLC procedures in 426 patients with a mean age of 72 years, and with 84% being male. Using final pathology as the reference standard, the sensitivity of white-light cystoscopy (WLC), BLC, and their

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combination for any malignant lesion was 75%, 90%, and 98.5%, respectively. The addition of BLC to standard WLC increased the detection rate by 12% for any papillary lesion and 44% for carcinoma in situ. Within the WLCs not identifying any lesions, an additional 170 lesions in 105 (25%) patients were detected exclusively with the addition of BLC. In addition, in patients with multifocal disease, BLC resulted in upstaging in 54 (13%) patients, leading to a change in management. The overall false-positive rate was 26% for WLC and 32% for BLC. Precisely 164 (39%) patients received Bacillus Calmette-Guerin at least 6 weeks prior to BLC, with a positive predictive value of BLC-detected malignancy being 55%. Among the positive/suspicious cytology patients who had no lesions on WLC (144 in total), BLC was able to detect an extra 57 malignant lesions in 36 of them, demonstrating a sensitivity of 92%. Only one mild dermatologic hypersensitivity reaction was noted (0.2%). Eventually, 40 (12%) patients eventually underwent cystectomy, four (10%) of whom did so exclusively because of lesions detected by BLC.

Summarizing these results, it seems that BLC has a significant increased detection rate of carcinoma in situ and papillary lesions when compared with WLC alone and is quite safe for use. Most importantly, BLC can lead to upstaging or upgrading in some 13% of patients. Lastly, recent Bacillus Calmette-Guerin therapy does not appear to impact BLC accuracy.

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E-Cigarette Smoke is potentially Bladder Carcinogenic- It Induces Tumorigenic DNA Adducts and Inhibits DNA Repair in Urothelial Cells

Since its introduction 2006 the popularity of the E-Cigarettes (ECE) in the US has exploded with approximately 12.6% of adults in the US reporting having tried an ECE. The naïve sense that ECE are safer than regular cigarettes has led a significant shift from regular tobacco cigarette use to smokeless tobacco without much evidence in regards to the its safety profile. More concerning is the rising use of smokeless tobacco by teenagers which lead the CDC to release a nationwide warning in 2014.

Dr. Moon-Shong Tang, from NYU School of Medicine, presents his work on the potential carcinogenic effect of smokeless cigarettes on the bladder. Dr. Tang explains although smokeless cigarettes are mostly concentrated nicotine; nicotine at high concentrations can be converted into nitrosamine compounds by a process called nitrosation. Nitrosamine compounds are well known urothelium carcinogens linked to the formation of bladder cancer in smokers. Since 90% of nicotine and its by-products are excreted by the kidneys the bladder is a perfect experimental model to for the study.

The study was performed in 20 mice which were randomized to ECE (10mg/ml) or filtered air. Using immunochemical methods and high performance liquid chromatography (HPLC) the urine was tested for common tobacco related carcinogens. DNA repair activity was assessed by an in vitro DNA-damage-dependent repair synthesis method and mutational susceptibility was determined with the supF system.

Mice exposed of ECS had high concentrations of γ-OH-PdG and O-meth-dg adducts which are known carcinogens. Evidence of both DNA repair disruption and high mutation profiles were seen in the treated group.

In conclusion, E-Cigarettes have the potential to be carcinogenic to the bladder urothelium by induction of DNA damage and inhibition of DNA repair. More work needs to be done to validate this findings and asses if there is a dose dependent phenomenon as with regular tobacco. This findings are of great concern given the popularity of E-Cigarettes in adults and teenagers. If guidelines and warnings are not set in place we may be facing another cancer epidemic.

PRESENTED BY: MOON-SHONG TANG, PHD

INSTITUTION: NYU SCHOOL OF MEDICINE

WRITTEN BY: ANDRES F. CORREA, SOCIETY OF UROLOGIC ONCOLOGY FELLOW, FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Improved Recurrence Free Survival in NMIBC Patients Taking Metformin Demonstrates Dose Dependence

There has been published literature showing that Metformin may affect recurrence of non-muscle invasive bladder cancer (NMIBC). Dr. Timothy Rushmer presented a study that evaluated the association of Metformin among common prognostic factors for bladder cancer recurrence in a multivariate model and assessed whether Metformin demonstrates a dose dependent effect.

A single institutional database including 503 patients treated with transurethral resection (TUR) for NMIBC were initially analyzed. These patients were followed longitudinally having an additional 682 recurrences and subsequent TURs. Overall, 1185 TURs were performed on these 503 patients. A total of 144/503 cases of NMIBC TURs, in 60 unique patients, met the inclusion criteria and were taking Metformin at the time of TUR.

Results demonstrated that the median age was 70.6 years with a median time to recurrence of 15 months (IQR 6.18-35.6). On univariate analysis, factors associated with statistically significant improved recurrence free survival (RFS) included: metformin use at TUR (p=0.01, HR 0.61, 95% CI 0.42-0.89), metformin dose ≥2000 mg (p=0.03, HR 0.50, 95% CI 0.28-0.90), age, multifocality, tumor size, perioperative Mitomycin-C, bacillus Calmette-Guerin therapy, and intravesical chemotherapy. Multivariate analysis demonstrated improved RFS when comparing diabetic patients on metformin at

TUR to diabetic patients not on metformin (p=0.0002, HR 0.51, 95% CI 0.36-0.72) and improved RFS even when comparing diabetic patients on metformin to non-diabetic patients not on metformin (p=0.0001, HR 0.60, 95% CI 0.46-0.77). A separate multivariate analysis, demonstrated improved RFS when comparing patients taking ≥2000 mg of metformin to patients taking <2000 mg at the time of TUR (p=0.0054, HR 0.39, CI 0.20-0.76). The 5-year RFS rate was 42.3% for diabetic patients on metformin, 35.1% for non-diabetics not on metformin, and 9.7% for diabetic patients not treated with metformin (p=0.0001).

This study demonstrates a clear advantage for Metformin use at the time of TUR, being associated with improved 5 year RFS in a multivariate model. Additionally, Metformin dose ≥2000 mg is independently associated with improved RFS.

PRESENTED BY: TIMOTHY RUSHMER, MADISON, WI

WRITTEN BY: HANAN GOLDBERG, MD, UROLOGIC ONCOLOGY FELLOW (SUO), UNIVERSITY OF TORONTO, PRINCESS MARGARET CANCER CENTRE

Comparison of total 90 day costs for open versus robotic cystectomy

In this study analyzing the cost of extirpative treatment for bladder cancer, the investigators from UT MD Anderson Cancer Center retrospectively analyzed the cost of surgery and postoperative care in 100 pair wise matched open vs. robotic assisted radical cystectomy patients. The two groups had similar clinicopathologic features, neoadjuvant chemotherapy rates, and pathologic staging at radical cystectomy (RC). Robotic assisted radical cystectomy (RARC) was found to be more costly overall. Not surprisingly, most of the higher cost for RARC was found on the day of the operation. Furthermore, the cumulative cost remained higher than open RC throughout the follow up period of 90 days. The authors did find a decreased hospital length of stay, number of complications, blood loss and need for transfusions in the RARC group.

The study excluded patients undergoing neobladder creation as these patients are known to have higher rates of complication post-operatively, and may introduce bias in the comparative analysis. In addition, the investigators matched patients in both groups according to the year of surgery, in order to eliminate differences introduced in the postoperative protocol that may have affected hospital length of stay and complication rates. In the current cost-driven environment we operate, this study serves as an important benchmark for future practice in the care of patients with bladder cancer.

PRESENTED BY: MICHAEL J. METCALFE, MD

WRITTEN BY: ROGER LI MD UROLOGIC ONCOLOGY FELLOW, UT MD ANDERSON CANCER CENTER AND ASHISH M. KAMAT MD WAYNE B. DUDDLESTEN PROFESSOR, UT MD ANDERSON CANCER CENTER

Is compliance to an enhanced recovery protocol after radical cystectomy associated with improved post operative outcomes?

Enhanced recovery after surgery (ERAS) has been shown to shorten length of stay for patients undergoing radical cystectomy. The objective of this study was to confirm the compliance with an enhanced recovery program was associated with post-operative outcomes. They used a composite compliance score to determine if 18 interventions were associated with the improved outcomes for 303 patients.

Patients who had higher scores indicating a higher compliance were younger, had less blood transfusions, and shorter operative times. Multivariate analysis demonstrated higher compliance was associated with shorter length of stay, reduced GI complications (p<0.01) and 30-day high grade complications (0.026).

This is the latest study to confirm the benefits of an enhanced recovery pathway. Patients continue to demonstrate significant benefit from adherence to evidence based pathways to improve their perioperative care. This is the second study like this done this year that demonstrated quality improvement in cystectomy care with a compliance score for patients on enhanced recovery. Continued quality improvement for patients undergoing cystectomy is essential in improvement of the ultimate outcomes.

PRESENTED BY: SAUM GHODOUSSIPOUR, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, CA

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Adjuvant Sunitinib in Patients with High-Risk Renal Cell Carcinoma: Subgroup Analysis from S-TRAC Trial

Dr, Allan Pantuck presented a subgroup analysis from the adjuvant sunitinib treatment for patients at high risk of recurrence for renal cell carcinoma following nephrectomy (S-TRAC) trial. They were included in the study if they had completely resected stage T3 and higher clear cell renal cell carcinomas and were randomized to sunitnib 50 mg on a 4-week-on, 2-week-off schedule versus placebo (N Engl J Med. 2016;375:2246). The primary analysis demonstrated improved disease-free survival (DFS) for the sunitnib arm relative to placebo (hazard ratio 0.76, 95% confidence interval 0.59-0.98). There was no difference in recurrence patterns between the two arms.

Dr. Pantuck offered data specifically on patients with high Fuhrman grade (3 or higher) tumors and T3 or greater disease. Again, an improvement in DFS was observed for individuals in the sunitinib arm (6.2 years vs. 4.0 years, P < .05). The overall survival endpoint for this subgroup has not yet been met. He concluded that subgroup analyses are consistent with the primary analysis confirming a benefit in DFS favoring adjuvant sunitinib. With time, differences in overall survival may become more apparent.

PRESENTED BY: ALLAN PANTUCK, MD, UCLA, LOS ANGELES, CA

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

American Urological Association Guidelines 2017 Renal Cancer: Localized

The Cleveland Clinic's Dr. Steven Campbell presented the updated 2017 American Urological Association guidelines for localized kidney cancer. The most significant change to the guidelines is the lack of index patients as the panel recognized the great variance in patients' oncologic and functional characteristics. In the guidelines, the panel focused on the importance of functional outcomes as they are the greatest determinants of quality of life and survival since few patients with localized disease die of kidney cancer.

The panel emphasized the role of the urologist in patient counseling, which should address both oncologic and functional issues along with the assessment of competing risk to tailor management. The panel recommends the use of renal mass biopsy in cases where the renal mass is suspected of being hematologic, metastatic, inflammatory, or infectious in nature. In other cases, a detailed discussion about the risk and efficacy of renal mass biopsy should be had with each patient. If renal mass biopsy is performed, the recommended technique is for multiple core biopsies to be performed over fine needle aspiration.

With regard to treatment, for patients with cT1a renal masses (≤ 4 cm), partial nephrectomy (PN) should be the standard care via an open or laparoscopic approach. Several reports, including a randomized, controlled trial, have proven equivalent oncologic outcomes with a nephron-sparing approach compared with radical nephrectomy (RN). In addition, a majority of cT1a renal masses are either benign or low-grade malignancies in which an RN would be "treatment overkill." Physicians should prioritize PN in patients with an anatomic/functional solitary renal unit, those with known chronic kidney disease, or individuals with evidence of proteinuria. The use of PN is of great importance in patients with bilateral renal masses or a history of hereditary renal cell carcinoma syndromes. The technique by which a PN is accomplished, standard versus enucleation, remains unclear. Several retrospective reports have noted the safety of enucleation versus standard resection, but the data remains lacking, especially for high-grade masses.

RN should be offered to those who present with high tumor complexity in which PN would be unreasonable, even in experienced surgical hands. Ideally, the patient would have no history of significant chronic kidney disease (glomerular filtration rate ≤ 45) or evidence of proteinuria.

Thermal tumor ablation is recommended for individuals in whom PN is ill-advised due to competing medical comorbidities or because they are unwilling to accept the inherent risk of PN. The treating physician should counsel the patient on the available data that show thermal tumor ablation to be inferior to PN with regard to oncologic control as well as a high likelihood of repeat ablation being necessary.

Finally, active surveillance should be offered to those patients in which the competing risks outweigh the benefits of treatment or who are unwilling to undergo treatment. When considering active surveillance, the treating physician must discuss with the patient the expected treatment triggers and the very low but real risk of metastatic progression under surveillance.

PRESENTED BY: STEVEN CAMPBELL, MD, CLEVELAND CLINIC, CLEVELAND, OH

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Robot-Assisted Radical Nephrectomy and Inferior Vena Cava Thrombectomy: Surgical Technique and Perioperative and Oncologic Outcomes

Dr. Giuseppe Simone presented the University of Southern California experience with robotic inferior vena cava (IVC) thrombectomy. Some data have been reported earlier by this group, and the feasibility of the procedure seems to continue to improve. The data offered was from two tertiary referral centers over 5 years and including 35 patients. In his presentation, Dr. Simone described the surgical technique for levels 1, 2, and 3 thrombi via animated video.

The operative technique starts by ligating the renal artery. Next, the renal veins and IVC are occluded, and a small cavotomy is made to introduce a Fogarty catheter. This type of catheter is monitored

via transesophageal ultrasound and is inflated above the cephalad boundary of the tumor thrombus to occlude the superior aspect of the vena cava. The renal vein is then stapled (across the thrombus) and the kidney is removed. A cavotomy is made, and the remainder of the thrombus is delivered, followed by caval closure.

The presented outcomes appear similar, if not favorable, to open approaches to IVC thrombi. Only four patients had Grade 3 or higher complications, and there were no reported deaths during the study period. Of the patients undergoing surgery, 37% had cytoreductive nephrectomy and 63% underwent surgery with curative intent. Intriguingly, cytoreductive patients experienced a 2-year survival of 92%, whereas the curative-intent group had a survival of only 77% at 2 years. Clearly, the low patient numbers and the lack of prospective controls with patient matching likely led to the survival differences seen. Nonetheless, it does appear that with appropriately selected patients in either group, robotic thrombectomies may be a reasonable surgical option.

As expected with this new technique, several audience members had questions regarding the safety and efficacy of robotic assistance versus open surgical techniques for these complex cases. As the experience with these cases grows, the data will either prove this to be a safe and effective treatment option or they will lead us to abandon this approach. As surgeons improve their experience and techniques, however, it seems more likely that robotic nephrectomy/thrombectomy is here to stay.

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Active Surveillance for Cystic Renal Masses with 5 or More Years of Follow-Up

At the Uroradiology poster session at the 2017 American Urological Association Annual Meeting, the group from Fox Chase Cancer Center presented outcomes of their active surveillance (AS) cohort of patients with cystic renal masses, specifically those with long-term (>5 years) follow-up. Certainly with improved abdominal cross-sectional imaging, urologists and radiologists are increasingly seeing patients in the clinic with these specific mass characteristics.

Among 2574 in the Fox Chase Cancer Center prospectively maintained database, the authors identified 601 patients on AS, 196 of whom had cystic renal masses. The primary outcome of the study was that individuals subsequently underwent delayed intervention for their cystic renal mass. Those with cystic renal masses who were enrolled in AS were predominantly male (64.3%), had a median age of 64 years, and showed a mean estimated tumor volume of 39 cm3. The median follow-up for the cohort was 59.7 months, during which 48 patients (24%) underwent delayed intervention at a median time of 16.7 months, with the majority (64%) done within 2 years of diagnosis. Furthermore, individuals with cystic renal masses were less likely (33.9% vs. 23.3%, $P < .016$) to proceed to treatment when compared with patients with solid renal masses. The mean change in estimated tumor volume was 5.8 cm3/yr, which was slower when contrasted with solid masses (5.8 vs. 11.4 cm3/yr, $P < .04$). Importantly, 95% of patients were alive at 60 months of follow-up, and only one of them developed distant metastasis. A possible limitation of the study was that renal biopsy rates and pathologic diagnosis for those patients undergoing renal biopsy were not provided.

The authors concluded that AS with or without delayed intervention is a successful strategy in well-selected patients with localized cystic renal masses and that most people who are slated to receive delayed intervention will do so within the first 2 years on AS. The results presented were important when considering the potential for overtreatment of these typically indolent renal lesions. Similar results suggested a benign course for cystic renal masses that would be presented later during the American Urological Association 2017 Annual Meeting.[1]

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REFERENCE

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Survival Following Neoadjuvant Targeted Therapy and Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma Patients

Dr. Shivashankar Damodaran and colleagues from this multi-institutional series performed a rather interesting retrospective analysis of patients with metastatic renal cell carcinoma who underwent cytoreductive nephrectomy (CN), comparing groups that underwent upfront CN with those who had presurgical targeted therapy (PTT) prior to CN. Previous studies on the effect of PTT on tumor and thrombus characteristics in advanced renal cell carcinomapatients did not show any differences in thrombus level or other tumor characteristics, indicating that targeted therapy may not have immediate local effects on these tumors. Another pertinent question that remains to be answered, however, is what the effect on survival is that PTT may confer to patients undergoing CN. Indeed, surgery is complex, and CN may be particularly risky for those with poor-risk disease characteristics. Hence, the question has merit.

The study's authors identified 486 patients between 2000 and 2015 from five cancer centers in the United States. The two groups being compared were those who received PTT prior to CN (8%) versus those who underwent upfront CN (92%). There were no differences between

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thrombus level or risk grouping by Memorial Sloan Kettering Cancer Center or International Metastatic Renal Cell Carcinoma Database Consortium risk-predicting models.

For patients undergoing PTT, median therapy time was 12 weeks, and most patients were treated with either sunitinib or bevacizumab. Similar to findings in previous studies, there was no difference in thrombus level for most patients following PTT. Median overall survival analysis showed no difference in PTT versus upfront CN (26.2 months vs. 24.6 months, respectively, P = .36). However, for individuals with International Metastatic Renal Cell Carcinoma Database Consortium poor-risk disease, there was a nonsignificant, but quite dramatic, difference in median overall survival for patients undergoing PTT versus upfront CN (38.1 months vs. 13.4 months, respectively, P = .28).

The authors concluded that while there did not appear to be a survival benefit (at least in this time period) for treatment with targeted therapy prior to CN, there may be a signal that poor-risk patients could potentially benefit from presurgical treatment.

While these findings were certainly exciting, especially if poor-risk patients may one day be proven to have improved outcomes following PTT, this study had its inherent limits. The retrospective nature of the study could not control for all biases that led to the selection of those who received therapy before surgery, and this limited the power of the conclusions. Furthermore, only 8% of the study's patients had PTT. Perhaps a more important result derived from this study was that PTT seemed not to have a major effect on survival outcomes, while CN itself showed a measurable benefit. With the current data, upfront CN seems the reasonable choice for most patients.

PRESENTED BY: SHIVASHANKAR DAMODARAN, MBMCH, AND COLLEAGUES, UNIVERSITY OF WISCONSIN

WRITTEN BY: SHREYAS JOSHI, MD, FOX CHASE CANCER CENTER, PHILADELPHIA, PA

The Re-emergence of Immunotherapy in Renal Cell Carcinoma and Novel Clinical Trials

The history of immunotherapy for the management of advanced renal cell carcinoma (RCC) has been hot and cold over the last 20 years. The introduction of programmed cell death-1 (PD-1) blockade therapy has revolutionized the treatment of advanced RCC and many other malignancies. PD-1 blockade therapy targets the acquired physiologic advantage of some tumor to escape immune system recognition by blocking the PD-L1/2 ligand and allowing T-cell recognition.

Checkmate-025 was the seminal trial that showed the survival benefit of nivolumab in patients with vascular endothelial growth factor refractory disease compared with everolimus (standard of care). Not only was nivolumab more efficacious, but it was better tolerated than everolimus. Although there was an increase in survival with nivolumab, a proportional tumor response rate was not seen, with only 1% of patients achieving a complete tumor response.

Several theories have been proposed for the lack of tumor response with PD-1 blockade therapy, which include inhibition of tumor antigen presentation, secretion of immunosuppressive factors by the tumor, alternative pathway for immune system inhibition, and recruitment of immunosuppressive cell types. This has led to the use of combination therapy to counteract some of these mechanisms.

The addition of vascular endothelial growth factor inhibitors has shown synergy with PD-1 blockade therapy by reducing immunosuppressive cell population and increasing T-cell infiltration into the tumors. A phase 2 study adding bevacizumab to atezolizumab versus sunitinib showed initial promise with an objective response rate of 41%. In the phase 2 study, the effect was blunted in newcomers, but it did show some benefit in patients with high PD-1 tumor expression. Another phase 2 trial assessed the effect of adding axitinib to pembrolizumab, which showed promising results with an overall response rate of 70%, with 94% of patients showing some type of tumor shrinkage. No new toxicities were noted in the study, and very few patients were terminated because of hepatotoxicity, which had been a concern.

There are numerous combination trials on the horizon, with the most exciting being the combination of cabozantinib and nivolumab. There are future trials that may include costimulator agents such as varlilumab (a CD27 agonist). Treatment with varlilumab has been linked to increase PD-L1/L2-ligand expression in cold tumors.

In conclusion, PD-1 blockade therapy has revolutionized the treatment of advanced RCC. Even with PD-1 blockade therapy, 30% of patients remain refractory to the treatment, likely from a variety of alternate mechanisms. A tremendous volume of clinical innovation is in progress assessing combination treatments and improving agent tolerability.

PRESENTED BY: LAUREN HARSHMAN, MD, BRIGHAM AND WOMEN'S HOSPITAL AND DANA-FARBER CANCER INSTITUTE

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Excised Parenchymal Mass and Devascularized Parenchymal Mass

Researchers from the Cleveland Clinic investigated the impact of devascularized tissue, both the excised mass and the residual mass, on functional outcomes following renal artery clamping during partial nephrectomy (PN). Using computed tomography, they defined the excised parenchymal mass (EPM) as specimen volume—tumor volume and the devascularized parenchymal mass (DPM) as total parenchymal mass loss—EPM. Their study's aim was to develop a method of measuring and evaluating how devascularized renal tissue during PN may or may not affect surgical outcomes.

The difference in the glomerular filtration rate preoperatively (74 mL/min/1.73m2) and postoperatively (67 mL/min/1.73m2) in their sample of 168 patients was not significant. Median EPM was 9 cc, DPM was 16 cc, and total parenchymal volume loss was 28 cc. On

average, EPM consisted of 5% of the preoperative renal parenchymal mass, and DPM consisted of 8.6% of the preoperative renal parenchymal mass. Preservation of the glomerular filtration rate occurred in 79% of patients. Overall, DPM and EPM correlated positively with the total parenchymal mass loss; however, the relationship with DPM was stronger.

The excision of a renal mass during PN requires renal artery clamping to maintain hemostasis and control visualization in PN. The results of this study identify the importance of the devascularized tissue mass remaining after renal clamping and excision with respect to the inevitable loss of nephron mass and renal function. This finding suggests that modification of surgical technique or other intraoperative interventions may be required to minimize the loss of devascularized tissue (ie, DPM) in an already compromised kidney affected by a neoplasm. Furthermore, a technique to measure and evaluate EPM and DPM is accomplished using computed tomography and can be part of assessing the functional outcomes of PN. These metrics also may be important indicators of the impact of further modifications to PN and the preservation of renal function.

PRESENTED BY: WEN DONG, MD

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The Effect of Anatomic Location of Retroperitoneal Lymph Node Metastases on Cancer-Specific Survival in Patients with Clear Cell Carcinoma

Lymphadenectomy at the time of radical nephrectomy has lost favor due to the increased use of laparoscopy, which makes lymphadenectomy technically challenging and time consuming. Furthermore, recent data from the Mayo Clinic has questioned the use of lymphadenectomy at the time of radical nephrectomy because of the lack of a survival benefit (B Gershman, et al. Eur Urol.). In his talk, Dr. Alessandro Nini presented data that assess the effect of anatomic location of lymph node metastases on cancer-specific survival in patients with clear cell renal cell carcinoma.

The authors performed a retrospective review of 415 patients who underwent radical nephrectomy with extended lymph node dissection (hilar, regional ipsilateral, and interaortocaval) at two tertiary referral centers in Italy.

Assessing node location in patients presenting with one positive node, researchers noted that 54% were in the ipsilateral nodal region and 26% in the interaortocaval region, which was different from individuals presenting with two or more positive lymph nodes, in which 56% of the nodal metastasis were observed in the interaortocaval area. With regard to tumor location, there was variation in the nodal distribution between right-sided and left-sided tumors. In right-sided tumors, 40% of positive nodes were discovered in the interaortocaval area and 44% in the ipsilateral lymph node packet. On the left side, 67% of positive nodes were seen in the ipsilateral lymph node packet, with only 9% found in the interaortocaval area. The laterality pattern becomes less heterogeneous in patients with two more positive lymph nodes, with 91% of nodal metastases located in the ipsilateral packet on the left side and 87% located in the interaortocaval area on right-sided tumors.

On survival analysis, the number of nodal metastases was not associated with worse cancer-specific survival. Concerning location, harboring nodal metastasis in the interaortocaval vicinity was associated with a worse cancer-specific survival odds ratio of 1.8 (1.0-3.2).

In conclusion, the data show there is no clear nodal spread pattern associated with renal cell carcinoma. Nodal metastasis located in the interaortocaval appears to be associated with worsening cancer-specific survival. While the study is provocative, it does have limitations that are mostly related to its retrospective nature and small sample size. This is clear in the assessment nodal location where nodal distribution changed significantly in patients presenting with a higher positive node burden. If the study is taken at its word, it seems to make the assessment that right-sided tumors appear to be more aggressive than left-sided tumors, given the higher propensity for having interaortocaval node involvement. Finally, the study does not help with clinical assessment as the analysis is based on patient's pathologic nodal status and not clinical nodal status. In the future, studies assessing clinical nodal location would be helpful in further answering this question.

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The Role of Neoadjuvant and Adjuvant Systemic Therapy in Renal Cell Carcinoma

Dr. Mohammad Allaf presented a comprehensive overview of the current state of understanding around neoadjuvant therapy (NAT) and adjuvant therapy (AT) for renal cancer. He started with an understandable plea to urologists to remain active participants in this space. The investigation of many new drugs and ATs falls within the urologists' realm.

Surgical monotherapy appears to fail to cure a significant proportion of "localized" renal cell carcinoma (RCC). In cancer, we just utilize NATt and AT to achieve a variety of outcomes. For RCC in specific, NAT has been used to try to shrink tumors and facilitate surgical intervention. AT is thought to control micrometastatic disease and reduce tumor recurrence risks.

There is mixed evidence as to the efficacy of NAT in the setting of renal tumor thrombus. A number of case series (largest N = 25) have

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found that approximately 40% of patients change their thrombus size, but very few change thrombus "level." Indeed, some thrombi continue to grow during NAT, and therapies do not come without their own toxicities.

On the other hand, retrospective series and phase II trials seem to show that NAT helps facilitate more effective surgical resection. Of those receiving NAT, about 25% may appreciate tumor size reduction, and some 50% can then receive a partial nephrectomy. This is a fantastic outcome, though there is clearly a bias when analyzing retrospective data with respect to who is chosen for surgery, etc. The bottom line for NAT is that there is limited, although encouraging, data showing a clinically meaningful effect on renal tumors, but this space is still experimental and requires more data.

The history of AT for RCC has largely been that of failure to achieve clinical impact. Chemotherapy, radiation, and combinations thereof dating back to the 1980s have consistently failed to show improvement in outcomes. The last few years has seen a rags-to-riches story in this area, though; and there are currently a number of adjuvant trials underway with a host of new agents. Highlighting the most high-profile and recently published studies, Dr. Allaf presented data from ASSURE, S-TRAC, and PROTECT.

ASSURE (sunitinib or sorafenib vs. placebo) was negative for overall or disease-free survival. S-TRAC (sunitinib vs. placebo) enrolled a slightly higher-risk patient population, finding that disease-free survival improved by about 1 year with treatment. Overall survival data had not matured by the time of publication. PROTECT (pazopanib vs. placebo) has not been completed, but early data suggest that it, too, will be a negative study.

Does this mean that we continue to have no hope for effective AT in high-risk RCC? Trials in this space are difficult, since accruing enough high-risk patients and following outcomes is challenging in RCC. ASSURE and S-TRAC had several important differences, but patients in both trials also experienced rather significant morbidity. About 60% of individuals in both trials endured Grades 3-4 toxicities, and 40% of patients in the two trials withdrew from the studies. So the bottom line at this stage is that AT is toxic and does not appear to have enough benefit to support clinical application. Several more phase III adjuvant trials are currently underway (SORCE, EVEREST, PROTECT, ATLAS) that may add more clarity to the answer to this question.

Several extremely exciting new immune checkpoint inhibitor trials are now in motion. These include: PROSPER (nivolumab vs. observation), IMmotion10 (atezolizumab vs. placebo), and KEYNOTE (pembrolizumab vs. placebo). Only PROSPER will be evaluated in the neoadjuvant space. Although there are key differences in each of these trial designs, investigators have learned important lessons from the past and we hope to gain clean and actionable data from these ongoing studies.

We should also not forget to push for more studies in the neoadjuvant area. The rationale for NAT is strong because of several key facts. There are most definitely ongoing anti-tumor T-cell responses in tumors. Nephrectomy will remove the vast majority of tumor cells and anti-tumor T-cells. Circulating programmed cell death-1 or PD-1+ cells significantly decrease following nephrectomy. Animal data suggest NAT is better than AT (primary tumor is required for expansion of tumor-specific T-cells). Ultimately, NAT plus AT may have the highest likelihood of successfully reducing tumor recurrence and improving survival in high-risk localized RCC.

This is a rapidly expanding space for research. Circling back to Dr. Allaf's plea, it is imperative that urologists remain involved and enthusiastically enroll eligible patients into these continuing trials. It is high time that we improve outcomes for high-risk RCC, and we may well be on the cusp of finding a multimodality treatment package that can achieve this dream.

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WRITTEN BY: SHREYAS JOSHI, MD, FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Predicting Renal Cell Carcinoma Progression After Surgery

The team from the Mayo Clinic sought to update predictive models for cancer progression for localized renal cell carcinoma (RCC) as most previous studies have been limited solely to clear cell carcinoma. However, this study sought to analyze several histologies: clear cell, papillary, and chromophobe RCC. A retrospective analysis of their institutional database was performed, using a multivariate model for progression-free survival (PFS) and cancer-specific survival (CSS) among patients with clear cell, papillary, and chromophobe RCC individually.

Over 3500 patients were identified and analyzed, with clear cell carcinoma representing 77% of the cohort. Based on a median follow-up of 9.9 years, constitutional symptoms, increasing grade, presence of coagulative necrosis, sarcomatoid differentiation, larger tumor size, perinephric or renal sinus fat invasion, tumor thrombus level, worse than T3 stage, and nodal status were statistically significant predictors of PFS. In addition to the aforementioned features, age at surgery and Eastern Cooperative Oncology Group performance status were also statistically significant predictors of CSS.

Some 17% of the cohort was papillary RCC with a median follow-up of 10.3 years. Grade, perinephric or renal sinus fat invasion, and tumor thrombus were statistically significant predictors of PFS and CSS. Lastly, 6% of the cohort was chromophobe with a median follow-up of 9.1 years. PFS was predicted by the presence of sarcomatoid differentiation, perinephric or renal sinus fat invasion, and nodal involvement. None of the factors were able to foresee CSS for chromophobe RCC.

These models are useful in counseling patients in survival outcomes for the various RCC subtypes and should be validated with future prospective studies.

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Phase 3 Randomized Trial of Intravenous Mannitol Versus Placebo Prior To Renal Ischemia During Partial Nephrectomy: Impact on Renal Function Outcomes

Renal function recovery is a key outcome of nephron sparing surgery (NSS) and mannitol has been used during NSS to reduce the extent of renal function loss as a result of surgery. However, the role of mannitol during NSS has not been prospectively tested or validated, and is based on limited preclinical data on animal models. Additionally, studies have shown that the use of mannitol not only lack benefits on postoperative renal function recovery, but it could also potentially lead to renal failure. In this study, Dr. Massimiliano Spaliviero and colleagues conducted a randomized controlled trial to compare the effects of mannitol versus placebo to protect against the effects of transient renal ischemia and to assess the impact on postoperative renal function in patients undergoing NSS for renal cell cancer.

Patients undergoing open or robot-assisted laparoscopic NSS were randomized to receive either mannitol or normal saline solution placebo, within 30 minutes prior to renal artery clamping. A standardized fluid management algorithm was used intraoperatively to maintain hemodynamic stability and urine output, and eGFR was obtained postoperatively at postoperative day 1 and 2, 6 weeks, and 6 months. The primary endpoint of the study was difference in eGFR at 6 months following surgery. A threshold of 6 units of eGFR was used to define clinical significance and two-tailed P-value and a 95% confidence interval (CI) for difference were determined.

Primary and secondary endpoint outcomes and comparison of observed eGFR means in the mannitol arm and placebo arm over the study period showed no significant difference.

Based on their results, the authors concluded that intravenous mannitol infusion during NSS does not lead to clinically relevant improvement in renal function outcomes and should be discontinued.

This poster was awarded best poster of the session.

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Society of Urologic Oncology: Cystic renal masses – Radiographic assessment and management

Dr. Vincenzo Ficarra provided a thorough review on cystic renal lesions and their management. He reminded the audience of the Bosniak criteria for characterizing cystic renal masses and that the likelihood of malignancy increases in lockstep with increasing Bosniak score.

To facilitate the case discussion, Dr. Ficarra presented two cases. The first was a 54-year old female with no comorbidities who presented with an incidentally detected complex 2cm Bosniak II lesion in the left kidney. Given the known incidence of malignancy at 20-25% in these lesions, the patient was followed with interval imaging. At 24 months, the tumor had increased in size and complexity to a 4cm Bosniak III lesion. At this point, Dr. Ficarra took time to recommend against biopsy in this population since the sensitivity approaches only 83%. Given the more than 50% chance of malignancy for Bosniak III lesions, the patient was taken to surgery where a partial nephrectomy was performed. Final pathology demonstrated clear cell renal cell carcinoma, Fuhrman grade 2, pT1a with negative surgical margins.

Case two was a 63-year old male patient with an asymptomatic Bosniak III lesions. Again, given the high risk of malignancy, the patient was taken to surgery where a partial nephrectomy was performed. Final pathology represented a multilocular cystic renal cell carcinoma. Recent data have demonstrated favorable survival outcomes in these patients (Bhatt et al. J Urol 2016;196: 1350).

In conclusion, Dr. Ficarra noted that CT, MRI, and contrast-enhanced US represent the diagnostic tools to characterize cystic renal lesions. Category IIF lesions must be followed, while, category III/IV lesions are high-risk for malignancy and must be resected (unless patient is not a surgical candidate). Partial nephrectomy should be recommended in this tumor with preferential consideration favoring a minimally invasive approach. Lastly, multilocular cystic renal cell carcinomas usually have an excellent prognosis.

PRESENTED BY: VINCENZO FICARRA, MD

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