Prostate Cancer Academy 2017 Summaries

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KEY WORDS

Prostate-specific antigen • Prostate cancer • Prostate biopsy • Tissue biomarkers • Magnetic resonance imaging • MRI targeted biopsy • Focal therapy • Radiation therapy • Androgen deprivation therapy • Positron emission tomography

The second annual Prostate Cancer Academy was held in Los Angeles, California, on October 13 and 14, 2017. This meeting brought together urology residents, fellows, members of LUGPA, and others to discuss the cutting edge in the management of prostate cancer. The program included didactic sessions as well as case-based discussions, both with an emphasis on interaction between faculty and program participants.

Improving Specificity of Prostate-specific Antigen Screening—Serum and Urine Markers: Who Doesn't Need a Prostate Biopsy?

Presented by Dan Lin, MD

Urology as a specialty has entered an era that mandates a decrease in prostate cancer overdiagnosis and overtreatment. For decades, urologists have relied on prostate-specific antigen (PSA) levels as a biomarker to detect prostate cancer. However, PSA alone is plagued by low specificity for detecting prostate cancer, leaving the door open for adjunct biomarkers that can be used to better identify men appropriate for biopsy (Table 1).

One such biomarker is Prostate Health Index (PHI). This blood test incorporates the different isoforms of PSA, including pro PSA, free PSA, and total PSA into a proprietary equation. This then generates a score that correlates to risk of prostate cancer on biopsy. PHI has been shown to outperform all the constituent isoforms of PSA when used separately. High PHI scores have been associated with aggressive prostate cancers, both on biopsy and prostatectomy. Alternatively, low PHI scores can lead to a reduction in prostate biopsies by 30%.

The 4Kscore® Test (OPKO Health, Miami, FL) is another assay used to stratify patients prior to biopsy. This blood test uses total PSA, free PSA, intact PSA, and human kallikrein-2, as well as clinical factors such as age, digital rectal examination (DRE) results, and prior biopsy status, to generate a percent risk for aggressive prostate cancer on biopsy. It also has been shown to correlate with poor pathologic features on radical prostatectomy (RP). Similar to PHI, the 4Kscore has the potential to reduce prostate biopsies by 30%.

TABLE 1

Biomarkers Available for Prostate Cancer Screening and Management

	PHI[a]	4Kscore[b]	Select MDx[c]	Confirm MDx[d]	Prolaris[e]	Oncotype Dx[f]	Decipher[g]
Setting	Prebiopsy	Prebiopsy	Prebiopsy	Repeat biopsy	Postbiopy; post-prostatectomy	Postprostatectomy	Postbiopsy; postprostatectomy
Sample	Blood	Blood	Post-DRE urine	Tissue	Tissue	Tissue	Tissue
Assay	Pro PSA, pre PSA, total PSA + clinical variables	Total PSA, free PSA, intact PSA, human kallekrein-2 + clinical variable	Measures *DLX1* and *HOXC6* expression	Measures DNA methylation	Measures expression of 31 cell-cycle progression genes	Measures 17 genes across 4 pathways	Measures 22 genes across the genome
Endpoint	Likelihood of Gleason ≥7 prostate cancer on biopsy	Likelihood of Gleason ≥7 prostate cancer on biopsy	Likelihood of Gleason ≥7 prostate cancer on initial biopsy	Likelihood of prostate cancer after initial negative biopsy result	Disease-specific and metastasis-free survival; risk of biochemical recurrence	Disease-specific and metastasis-free survival; likelihood of adverse pathology on RP	Risk of adverse pathology (Gleason ≥4); disease-specific and metastasis-free survival

[a]Beckman Coulter, Sharon Hill, PA.
[b]OPKO Health, Miami, FL.
[c]MDxHealth, Irvine, CA.
[d]MDxHealth, Irvine, CA.
[e]Myriad Genetic Laboratories, Salt Lake City, UT.
[f]Genomic Health, Redwood City, CA.
[g]GenomeDx, Vancouver, Canada.
DRE, digital rectal examination; PSA, prostate-specific antigen; RP, radical prostatectomy.

In addition to blood assays in the prebiopsy setting, physicians also have the option to use post-DRE urine-based testing. *PCA3* is a gene that is overexpressed in patients with prostate cancer and can be identified in the urine of men prior to biopsy. When used in the setting of prior negative biopsy results, it has a high negative predictive value, allowing the urologist to potentially forego repeat biopsies in some men. Select MDx (MDxHealth, Irvine, CA) is another urine assay used in this setting. It can detect messenger RNA of certain genes that are overexpressed in Gleason ≥7 prostate cancer. The results from Select MDx quote a percent risk of a prostate biopsy detecting both low- and high-grade prostate cancer. This test has a negative predictive value of 94% for high-grade disease and has been estimated to potentially reduce unnecessary biopsies by as much as 50%.

One of the newest and most exciting concepts in cancer detection is the idea of epigenetic abnormalities or "field effect" produced by solid tumors. ConfirmMDx (MDxHealth) is a tissue assay that detects DNA methylation in prostate tissue. High levels of DNA methylation suggest the presence of a nearby cancer despite a negative biopsy result. Alternatively, low levels of methylation have been shown to be associated with a 96% negative predictive value for high-grade prostate cancer, leading to a reduction in repeat prostate biopsies. This, in turn, has been projected to save approximately $600 per patient in healthcare spending.

Although there are many new tests available to urologists to improve prostate cancer screening, they are often costly and are not always covered by insurance. Another strategy that has been proposed to reduce overdiagnosis is to use a single PSA level obtained between age 44 and 50 years to drive future screening decisions. Men with a PSA value <1 before age 50 are at significantly lower risk of ever developing advanced disease and can likely be screened on a much less intensive schedule, if at all. This type of screening strategy is supported by the National Comprehensive Cancer Network guidelines.

The biomarkers mentioned in this section are all highly reliable promising adjuncts to PSA screening with high negative predictive values. Regardless of the tool chosen, urologists and patients alike must understand and accept that a small but non-zero percentage of high-grade cancers will be missed.

Despite this, practitioners would be wise to incorporate these assays into their practice in the continued effort to reduce the significant morbidity of unnecessary biopsies as well as the morbidity associated with overtreatment.

Risk Stratifying Low-risk Disease: Molecular Markers

Presented by Dan Lin, MD

Once a diagnosis of prostate cancer is made, how can one stratify patients into those that are appropriate for surveillance and those that would benefit from treatment? The four main biomarkers available in this space are Prolaris® (Myriad Genetic Laboratories, Salt Lake City, UT), OncotypeDx® (Genomic Health, Redwood City, CA), Decipher® (GenomeDx, Vancouver, Canada), and ProMark® (Metamark Genetics, Waltham, MA). All four are tissue assays that rely on gene sequencing to detect adverse biologic features. However, these tests have variable endpoints, making a certain test more or less useful depending on the specific clinical scenario.

Prolaris uses a 31-gene cell cycle progression signature from prostate biopsy tissue to predict prostate cancer-specific mortality at 10 years. A recent study by Shore and colleagues[1] found that performing a Prolaris assay resulted in a change in treatment decision in almost 50% of 1206 patients with prostate cancer, regardless of clinical risk category; 72% of these changes were decreases in treatment, whereas the rest were increases.

OncotypeDx measures the expression of 17 genes across four important genetic pathways, which include stromal response, androgen signaling, cell organization, and cell proliferation. This provides a Genomic Prostate Score™ that is an indicator of the biologic aggressiveness of the disease. This score has been validated to predict the risk of upgrading or upstaging at prostatectomy, thereby helping urologists and their patients decide between active surveillance and immediate treatment.[2]

Decipher measures the expression level of 22 genes across the entire genome that are shown to be involved in the development and progression of prostate cancer. This test has been validated to calculate the probability of clinical metastasis 5 years after RP. There are also significant data that suggest a genomic classifier may help select between adjuvant and salvage radiation for men with adverse pathologic features on prostatectomy.[3]

Although these tissue biomarkers clearly have some clinical utility and have been validated extensively in low-risk disease, many questions remain. Which low-risk patients will truly experience a clinical benefit? Are endpoints such as risk of metastasis and 10-year cancer-specific mortality useful for men with low-risk prostate cancer? What are the total cost savings (or costs incurred) to the system by using these tests? These tests should be used selectively as it is likely only a small percentage of men with Gleason $\leq 3+4=7$ disease—those with high-volume, low-risk disease or low-volume, intermediate-risk disease—will truly benefit from the addition of these assays.

The Role of Magnetic Resonance Imaging in Prostate Biopsy: Who and How to Biopsy?

Presented by Samir Taneja, MD

Over the past two decades, the use of magnetic resonance imaging (MRI) for prostate cancer has evolved dramatically. Although it began as a staging tool for men with biopsy-proven prostate cancer, it is now used for pre- and postbiopsy disease localization. Ultimately, it may be used for risk stratification, potentially as a biomarker for prediction of grade, stage, and clinical outcome in men with prostate cancer. For an MRI of the prostate to be most useful, it must be multiparametric and include T2-weighted images, diffusion-weighted images, and dynamic contrast-enhanced images.

The rationale behind using prostate MRI today is to better inform urologists regarding whom to biopsy and help identify and localize clinically significant cancer when the decision to biopsy is made. It facilitates treatment planning for radical surgery as well as focal therapy. Prostate MRI is equally important as a tool to avoid the morbidity of excess biopsies and avoid the overdetection of clinically indolent cancer. The hope is that the use of MRI will eventually prove to be cost effective by reducing unnecessary additional testing.

New York University (NYU; New York, NY) has one of the largest cohorts of men biopsied with an MRI/ultrasound (US) fusion biopsy system after having a prebiopsy MRI. Data from this cohort lends insight into both the utility and the limitations of prostate MRI and the MRI/US fusion platform. In the entire cohort of 746 men, MRI/US fusion biopsy was significantly better at detecting Gleason ≥ 7 disease (26% vs 20%) but worse at detecting Gleason 6 disease (13% vs 20%) than standard biopsy. Data from this cohort also clearly demonstrate that cancer detection rates vary widely based on the indication for biopsy in men with MRI targets having a suspicion score of 3 or 4 (Figure 1).

In men with prior negative biopsy results, MRI should be strongly considered prior to any subsequent

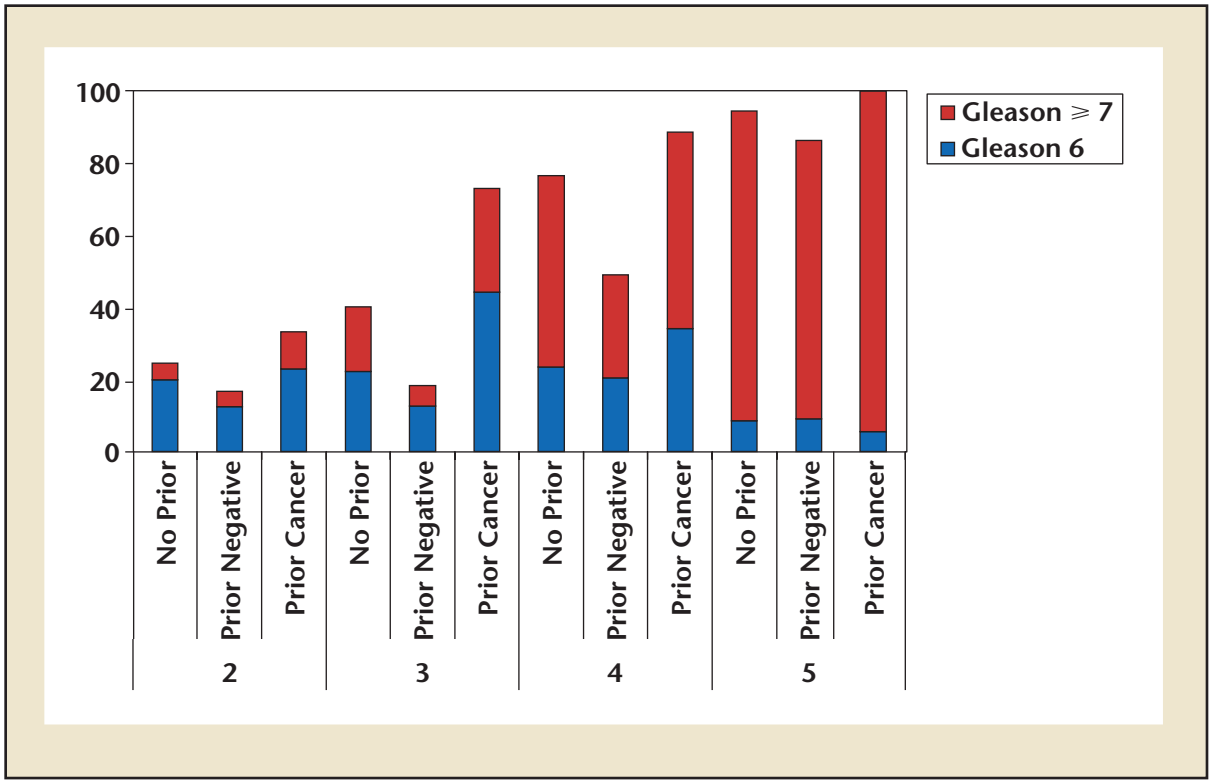

Figure 1. Prostate cancer detection rates based on indication and magnetic resonance imaging suspicion score. Data from Meng X et al.[19]

biopsies, as it can help to detect anterior or apical cancers missed by initial biopsy. Fusion biopsy in these men detects significantly more Gleason ≥7 cancers than standard biopsy. It may be possible to omit standard biopsy in this population, as it does not appear to contribute much to the detection of clinically significant disease.

In men with no previous biopsy, both targeted and systematic biopsies appear to contribute to cancer detection. Although targeted biopsy detects more clinically significant cancers, it still misses a small percentage of Gleason ≥7 cancers that are picked up by standard biopsy. As long as both targeted and standard biopsies are done together, it will be difficult to eliminate the overdetection of indolent disease associated with standard biopsy. Men who have lower suspicion lesions on MRI may be the most favorable cohort in whom to attempt targeted biopsy alone, especially in conjunction with other available biomarkers.

In men on active surveillance, MRI has a role in baseline risk stratification and can potentially reduce the number of biopsies required while on surveillance. At NYU, the Taneja protocol requires that men receive yearly MRI, a confirmatory targeted + standard biopsy at year 1, then again only at year 6, unless a for-cause biopsy is indicated earlier. Using this protocol, 78% of 263 men remain on active surveillance after 3 years of follow-up.

Focal Ablation of Prostate Cancer: Is It Ready for Prime Time?

Presented by Herbert Lepor, MD

Focal ablation is the destruction of a portion of prostate tissue using some kind of physical energy (eg, cryotherapy, high-frequency ultrasound, laser). The extent of the ablation can include a truly focal area, a hemiablation, or a "hockey stick" ablation. This type of therapy has emerged in the past decade or so as a response to the shifting paradigm of reducing the harms of radical treatment for prostate cancer. The primary advantages of focal therapy include the lower morbidity when compared with radical surgery, less damage to structures surrounding the prostate, and lower cost. The primary disadvantage remains the unclear long-term oncologic outcomes.

One key tenet on which focal ablation is predicated is the ability to accurately detect the index lesion on prostate imaging. It is therefore mandatory to have high-quality MRI and an experienced radiologist in place when attempting to start a focal therapy program. It is also important to understand that MRI and targeted biopsy do miss a portion of significant prostate cancers initially, and may also miss residual cancer in the postablation

setting. It is clear that a focal ablation must include at least a 10-mm margin around the target lesion on MRI to increase oncologic efficacy.

Oncologic efficacy remains the single biggest concern with regard to focal ablation. The first hurdle relates to retaining patients for follow-up biopsies so that cancer control can be confirmed. Because of the low side-effect profile of focal ablation, many men feel good after their ablative therapy and never return for follow-up, falsely assuming that their therapy was "successful." For men who do undergo postablation biopsies, the experience at NYU reveals that there is clearly a proportion of men who will have residual Gleason 6 disease and some with residual Gleason pattern 4. Still, the definition of failure is not clear cut, as many of these men qualify for active surveillance according to currently existing protocols.

Many questions remain unanswered regarding focal ablation. Which is the optimal energy source to use? What is the appropriate extent of the ablation zone? What is the best method to monitor for postablation success or failure? And, what will the intermediate- and long-term clinical outcomes be? When synthesizing all the data thus far, focal therapy does not appear to be ready for prime time, but it is certainly ready for clinical investigation.

2018 Radiation Oncology for Prostate Cancer Primer

Presented by
Steven Finkelstein, MD

Radiation therapy is employed as a single agent or part of a multimodal treatment plan in many men with prostate cancer. It is given in fractionated doses—a concept that stems from the fact that normal cells are better able to repair the double-strand DNA breaks that radiation causes. Radiation can be delivered externally, using a linear accelerator, as with external beam radiation therapy (EBRT), or internally, with implants or "seeds" that emit radiation. This is called brachytherapy. EBRT is most often used today and can imply any of many different treatments within this broad category. These include three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), proton beam therapy, and stereotactic body radiation therapy (SBRT).

3D-CRT and IMRT are both specialized forms of EBRT that modulate the radiation delivered to the surrounding structures to minimize toxicity. Proton beam therapy uses the different physical principles of protons to deliver more precise radiation to the target organ. However, side-effect profiles seem to be favorable for IMRT when compared to proton beam therapy (Figure 2). Regardless of therapy chosen, it is important to administer between 77 to 81 Gy to the prostate. Higher doses may result in improved oncologic control, but at the expense of increased toxicity.

SBRT utilizes a concept called hypofractionation to deliver high doses of radiation per fraction to achieve an overall shorter course of therapy. This allows for increased convenience to patients, decreased

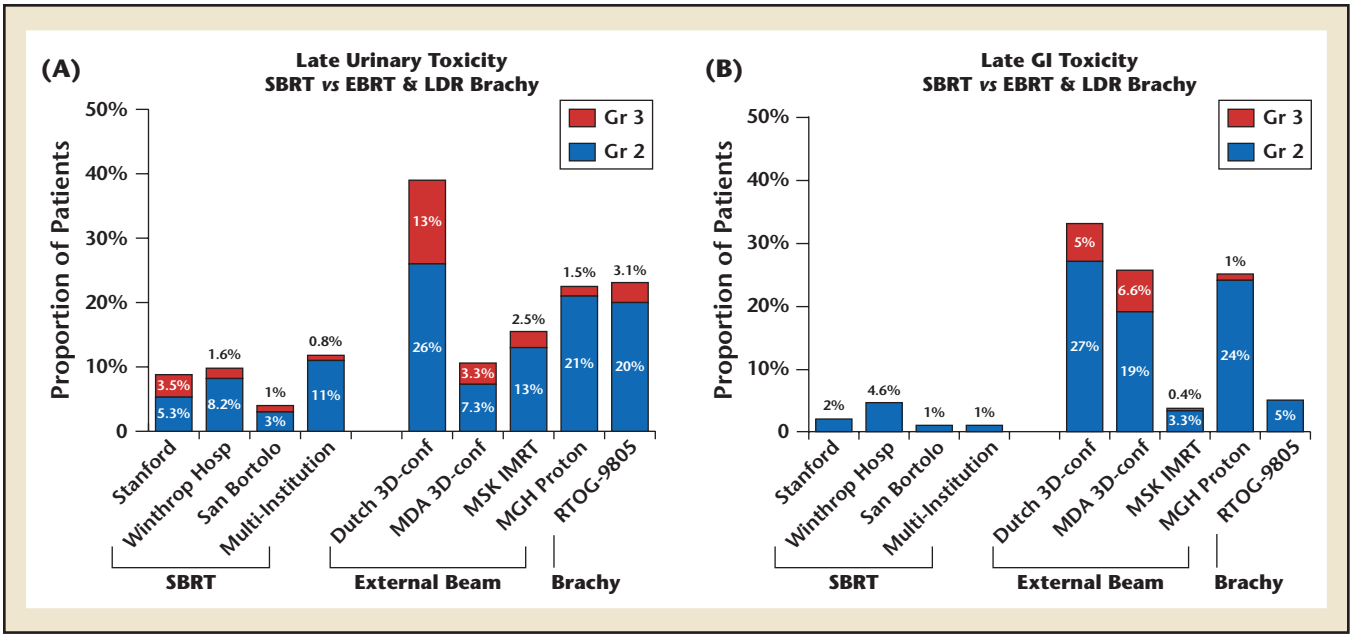

Figure 2. Side effects of radiation therapy. Brachy, brachytherapy; EBRT, external beam radiation therapy; GI, gastrointestinal; Gr, Gray; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy; LDR, low-dose rate; MGH, Massachusetts General Hospital; MSK, Memorial Sloan Kettering; RTOG, Radiation Therapy Oncology Group. Data from Meier R.[20]

costs, and lower long-term morbidity, but is associated with increased rates of immediate genitourinary toxicity, on par with brachytherapy.[4] SBRT is currently regarded as an acceptable option for patients with low- to intermediate-risk prostate cancer.

Optimal Treatment of Patients With High-risk Prostate Cancer

Presented by
Christopher Kane, MD

As screening practices have changed, men are again presenting with higher-risk and more advanced prostate cancers. The optimal management of high-risk prostate cancer continues to evolve, but there is significant evidence that men receiving radical surgery fare better in the long term than those who receive radiation. This advantage may be related to the fact that these men are likely to receive more effective multimodal therapy. The advantage of radical surgery disappears when considering men with low- and intermediate-risk disease, as well as men with multiple comorbidities.

When it comes to robotic versus open RP, cancer outcomes are likely more related to surgeon experience than operative approach. However, a concerning trend exists between surgeons performing robotic prostatectomy and a lower likelihood of completing a lymph node dissection. A thorough lymph node dissection is especially important in men with high-risk disease, as this aids pathologic staging. Also, we know that approximately 30% of men with positive lymph nodes will have long-term biochemical-free survival with surgery and lymphadenectomy alone. Men with two or fewer positive nodes are more likely to be in this favorable category.[5]

Men with locally advanced prostate cancer should be counseled about the advantage of multimodal treatment with radiation and androgen deprivation therapy (ADT). The addition of radiation appears also to benefit men with lymph-node–positive disease. Furthermore, the finding of a positive intraoperative lymph node should not preclude surgery if technically feasible. Men who had prostatectomy completed fared significantly better than those in whom surgery was aborted.[6]

An interesting area of research is the utility of local therapy in metastatic prostate cancer. The rationale for treatment is multifaceted but involves preventing the morbidity of local progression. There is also a belief that treating the primary tumor may alter the underlying tumor biology. Although there is no Level 1 evidence, there is a growing body of retrospective data that suggest adding radiation therapy or prostatectomy to ADT in metastatic prostate cancer will improve overall survival.[7,8] Men are currently being accrued for a clinical trial that will test this hypothesis in a prospective, randomized fashion.

Advances in Positron Emission Tomography Imaging

Presented by Philip Koo, MD

Methods to detect and localize prostate cancer metastases have advanced substantially since the development of bone scans in the 1970s. Standard bone scans have relatively low sensitivity, can have false-positive results, and are not good for assessing response to therapy. Furthermore, they do not provide any information on soft tissue disease. Contemporary imaging modalities are highly sensitive and are able to synthesize bone and soft tissue imaging into one examination.

C11-choline positron emission tomography (PET) is very sensitive for the detection of prostate cancer metastases and was U.S. Food and Drug Administration approved for this indication in 2012. Unfortunately, its short half-life of 20 minutes requires an on-site cyclotron and makes this test impractical for most centers. ^{18}F-fluciclovine PET is another form of imaging that was approved in 2016 for detection of prostate cancer metastasis. This test performs at least as well as C11-choline PET, but has a substantially longer half-life of 2 hours, making it much more commercially viable.

The latest development in PET imaging is prostate-specific membrane antigen (PSMA) PET/computed tomography. This uses a radiolabeled isotope to bind specifically to prostate cancer cells, making this test highly sensitive and specific. PSMA scanning has already been shown to be highly accurate in the identification of metastatic lymph nodes in men with biochemical recurrence undergoing salvage lymphadenectomy.[9] It also opens the door for theranostics, which is the fusion of diagnostic imaging with therapeutic intervention. The adoption of these expensive new imaging modalities into mainstream practice will depend partially on reimbursement and partially on their impact on clinical outcomes, which remains unknown.

Gonadotropin-releasing Hormone Agonists Versus Antagonists

Presented by
E. David Crawford, MD

Currently, there are many available agents that can achieve castration. These include estrogens, gonadotropin-releasing hormone (GnRH) agonists and antagonists, antiandrogens, and surgical

castration. Each has its advantages and drawbacks.

The use of estrogens is limited by their cardiovascular side effects. Surgical castration is a highly cost-effective, physiologically effective, rapid way of achieving androgen deprivation, but is limited by low acceptance by patients. Also, surgical castration is associated with high follicle-stimulating hormone (FSH) levels, which have been shown to accelerate tumor growth via angiogenesis. First- and second-generation antiandrogens alone are not as efficacious as other agents, and are associated with worse overall survival and gynecomastia.

Likely the most widely used agents are the GnRH agonists, such as leuprolide. They are more effective than estrogen and equivalent to orchiectomy in terms of overall survival. They are available in many formulations including long-lasting depots. However, they are also associated with testosterone flare when used without an antiandrogen, testosterone microsurges, testosterone escapes, and testosterone failures. More than half of patients experience testosterone escapes >20 ng/dL during treatment. This may be associated with worse outcomes, as testosterone goals <20 ng/dL have been associated with better PSA progression-free survival (PFS).

GnRH antagonists such as degarelix are the most novel agents developed for ADT. They achieve rapid and prolonged suppression of FSH, luteinizing hormone, and testosterone, and are not associated with testosterone flare or microsurges. Degarelix is also associated with improved PSA PFS when compared with leuprolide. This benefit translated to men initially on leuprolide in a crossover trial.[10] Furthermore, GnRH antagonists have been shown to have a reduced incidence of cardiovascular events when compared with GnRH agonists.[11]

Infusion Therapies and Advanced Prostate Cancer: The Role of the Urologist

Presented by Neal D. Shore, MD

Prior to 2010, the primary therapeutic options for advanced prostate cancer were ADT, docetaxel, and palliative chemotherapy for end-stage disease. Since then, there has been an explosion of new options that are available to the urologist in this disease space. Fortunately, for men with advanced prostate cancer, these drugs have the potential to improve both the quality and quantity of life.

Sipuleucel-T is one of the first immunotherapeutic agents approved for the treatment of cancer. It works by activating the patient's own immune system to fight prostate cancer cells via a process of leukapheresis, priming of antigen-presenting cells in the laboratory, and subsequent infusion of these cells back into the patient. These primed antigen-presenting cells then activate the patient's own T cells, which in turn attack and kill prostate cancer cells. This therapy is indicated for metastatic, asymptomatic, or minimally symptomatic castration-resistant prostate cancer (CRPC) and has been shown to increase survival by an average of 4 months in a randomized clinical trial. Advantages of this therapy include the favorable adverse-event profile and short 4- to 6-week treatment course. The main disadvantage of this therapy is that it does not affect PSA levels; therefore, there is currently no way to measure response to treatment. Studies are currently underway to identify men who are more likely to experience good response.

Radium-223 is another useful therapeutic agent indicated for men with CRPC and symptomatic bone metastases, without visceral metastases. It is an α-particle–emitting radioactive substance that is preferentially accumulated in bone due to its chemical similarity with calcium. It has been shown to increase overall survival by an average of 4 months in a randomized controlled trial. In general, it is very well tolerated by patients, but physicians must be aware of potential bone marrow suppression resulting in anemia, thrombocytopenia, or neutropenia.

Cabazitaxel is a microtubule inhibitor that is used in combination with prednisone for patients who have progressed on docetaxel. In a randomized clinical trial, cabazitaxel improved overall survival by 2.4 months over mitoxantrone. It is a drug with serious potential toxicities, primarily neutropenia, for which patients should be monitored closely. When compared with docetaxel it showed no improvement in survival, but it appeared to be better tolerated with less fatigue and less neuropathy.

Although these new infusion therapies for prostate cancer are immensely important in increasing survival, there are many questions left unanswered. Despite continuous advances, we still do not know the best sequence in which to give these drugs. We do not know whether giving one, or two, or three drugs in combination is superior to giving the drugs separately. Perhaps most importantly, we do not know which patients respond best to which treatments. Prostate cancer is a heterogeneous disease and we are currently doing very little in terms of individualizing therapy. To continue improving outcomes in metastatic CRPC, researchers hope to find biomarkers that will

identify men who would benefit most from a certain therapy.

One recently described example in the literature is androgen receptor splice-variant 7 (AR-V7). The presence of AR-V7 in circulating tumor cells in men with metastatic CRPC is predictive of a poor response to abiraterone and enzalutamide.[12] In contrast, taxanes appear to have a preserved response.[13] Stemming from these findings, it appears that AR-V7 may be a treatment selection marker in patients with metastatic CRPC, bringing us one step closer to personalized medicine.

Castration-resistant Prostate Cancer: Oral Therapeutics

Presented by Neal D. Shore, MD

ADT has been the cornerstone of treatment for metastatic prostate cancer for many decades. We have known about the effects of androgen ablation on prostate cell growth since the experiments of Huggins and Hodges in 1941. However, more recently, we have come to understand that prostate cancer cells make their own androgens and can even overexpress androgen receptors in the castration-resistant state. Although ADT does reliably reduce androgen levels to a low level, further reduction of circulating androgens with new agents such as abiraterone and enzalutamide provides a treatment benefit in CRPC.

Abiraterone is an androgen biosynthesis inhibitor that blocks the CYP17 enzyme. There is a resultant significant suppression of circulating androgens as well as an increase in mineralocorticoids, which is responsible for the side effects of hypertension, fluid retention, and hypokalemia that can be seen with this drug. In order to moderate the mineralocorticoid effect, abiraterone should be given in combination with prednisone. Abiraterone was first approved in the postchemotherapy setting after showing a 4-month overall survival benefit over placebo in a randomized clinical trial.[14] Later, abiraterone was also shown to provide a significant improvement over placebo in a chemotherapy-naïve population of men with CRPC,[15] and is most often used in this setting today.

Enzalutamide is an androgen receptor blocker and is another oral therapeutic option for metastatic prostate cancer. Unlike the first-generation antiandrogens such as flutamide and bicalutamide, enzalutamide irreversibly binds to the androgen receptor and has essentially no agonist activity. The results from the AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy) trial demonstrated a 5-month overall-survival benefit in the postchemotherapy setting for enzalutamide over placebo.[16] Similar to abiraterone, enzalutamide was then shown to be greatly more effective than placebo in chemotherapy-naive men in a subsequent trial.[17] Seizures have occurred in a small number of patients on enzalutamide.

Although these new oral therapeutics clearly have cemented an important role in the treatment of metastatic prostate cancer, the optimal way to deploy these drugs is unclear. There is some evidence that enzalutamide after abiraterone may be more effective than the converse, but data are limited by its retrospective nature. The effectiveness of combination therapy is also being tested. There is currently a randomized trial underway that is comparing therapy with abiraterone and enzalutamide to enzalutamide alone in patients with metastatic CRPC. Finally, there are questions regarding the timing of oral therapeutics in relation to chemotherapy.

Managing Bone Health in Advanced Prostate Cancer

Presented by Stephen Freedland, MD

Bone health is a critical and often underappreciated aspect of the care of men with metastatic prostate cancer. Men on ADT lose approximately 3% of their total bone mineral density after only 1 year of therapy. The bone loss per year in men on ADT is double that seen in menopausal women. Furthermore, the risk of pathologic fracture increases with increasing dosage of ADT over time.

Men starting on ADT should be assessed for baseline osteoporosis and for risks associated with developing osteoporosis in the future. These risks include family history of osteoporosis, personal history of fractures, smoking, heavy alcohol consumption, low body mass index, low vitamin D levels, and steroid use. Calcium and vitamin D have traditionally been prescribed for men starting ADT, but the utility of supplementation alone has never been proven in this subset of patients.

Other treatments available for men on ADT include a very low-carbohydrate diet that serves to block insulin resistance, bisphosphonates such as zoledronic acid, and a human monoclonal antibody called denosumab, which binds RANK (receptor activator of nuclear factor κ-B) ligand and prevents maturity of osteoclasts. In a large randomized trial of men with metastatic prostate cancer and bone metastases, denosumab had a longer time to first skeletal-related event (20.7 vs 17.1 mo) than zoledronic acid.[18] In addition to being

slightly more efficacious, it is also easier to administer given its subcutaneous dosing. Osteonecrosis of the jaw is a serious side effect that can occur with denosumab. ■

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