Treatment and Management of Patients With Prostate Cancer

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The following is a lightly edited manuscript of a teleconference discussion on treating patients with localized prostate cancer in the VHA.

PSA SCREENING

William J. Aronson, MD. I'm very encouraged that the U.S. Preventive Services Task Force (USPSTF) has recently drafted revised guidelines for screening men for prostate cancer in which they now are proposing a C grade for prostate specific antigen (PSA) screening in men aged < 70 years. In this age group they now propose an informed discussion with the patient regarding the pros and cons of screening (shared decision making). The USPSTF recommended against PSA screening in men aged ≥ 75 years in 2008 (D grade), and they recommended against PSA screening in all men in 2012 (D grade). Previously the USPSTF put a great deal of emphasis on the PLCO (Prostate, Lung, Colorectal, and Ovarian Screening Trial). In that trial, there was no difference in prostate cancer mortality between the study groups, but, it appears that up to 90% of men in the control group received PSA screening, therefore, invalidating the studies findings.

I still have serious concerns about giving a D grade for men aged > 70 years. Dr. Jim Hu from Cornell University recently published a study in *JAMA Oncology* and reported that men aged > 74 years now have twice the rate (12%) of presenting with metastatic disease at the time of diagnosis compared with men aged > 74 years prior to the 2008 USPSTF recommendations. In my view, otherwise healthy men with a good life expectancy, even if they're aged > 70 years, should still have an informed discussion with their physician about getting PSA screening.

Julie N. Graff, MD. I completely agree with Dr. Aronson, and I would add that our veterans are a special group of patients who have risk factors that aren't seen in the general population. For example, Agent Orange exposure, and I think the VA has not necessarily embraced those recommendations. I'd also add that people are living longer, and most of the men who die of prostate cancer are over the age of 80 years. We need to consider each patient individually and his life expectancy. It's okay to diagnose someone with prostate cancer, and it's important to have a conversation about how likely that cancer is to shorten his life and not just turn a blind eye to it.

Nicholas G. Nickols, MD, PhD. I don't think there's really anything clinically meaningful about PSA screening that can be gleaned from the PLCO trial. However, there was another trial that looked at PSA screening, the ERSPC (European Randomized Study of Screening for Prostate Cancer) trial, and had less contamination in the nonscreened arm and actually did ultimately show a 27% reduction in prostate cancer mortality in the screened men. We also know that local treatment in men with high-risk prostate cancer actually improves survival. By not screening, men with high-risk disease are going to miss out on potentially curative therapy.

Dr. Aronson. I think other endpoints are crucial to consider beyond just survival. Once patients have metastatic disease that can markedly impact their quality of life. Also, patients who are starting androgen deprivation therapy (ADT) have very significant issues with quality of life as well. I believe these other endpoints should also be considered by the USPSTF.

Jenna M. Houranieh, PharmD, BCOP. The American Cancer Society, ASCO (American Society of Clinical Oncology), NCCN (National Comprehensive Cancer Network), and the American Urological Association all had a different view on screening compared with the USPSTF that I think go more in line with some of the ways that we practice, because they take into consideration life expectancy, patients' risks, and the age of screening as well.

Discussion Participants

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ACTIVE SURVEILLANCE

Dr. Aronson. Active surveillance is now a well-established, reasonable approach to managing patients with low-risk prostate cancer. When we talk about the various treatment options, we always include a discussion of active surveillance and watchful waiting. Certainly, patients who have a Gleason score of 3+3, a low PSA (< 10) and low volume disease are ideal candidates for active surveillance. There is no established protocol for active surveillance, though there are a number of large series that report specific ways to go about doing it. The key issue for patients is to deemphasize the importance of the PSA, which is a very poor tool for monitoring progression of prostate cancer in men on active surveillance, and to focus on periodically obtaining prostate biopsies.

For patients with prostate cancer who have multiple medical problems and limited life expectancy, there is no reason to do biopsies on a regular basis. Watchful waiting would be more appropriate for these patients. One key issue, which is challenging right now, is that probably the best way to do active surveillance is with the more sophisticated biopsy technology that is now available. That includes both fusing magnetic resonance imaging (MRI) of the prostate into the ultrasound unit we are using to perform transrectal prostate biopsies. The more advanced biopsy units also provide the ability to perform same-site biopsies. There are specific coordinates at each site where a biopsy is performed so that we can go back to that same site on subsequent biopsies. Due to cost issues, these advanced biopsy units are not yet being used at a high frequency.

Dr. Nickols. The large ProtecT trial in the UK randomized men diagnosed with prostate cancer out of a PSA screening cohort to an active surveillance arm, a radical prostatectomy arm, and a radical radiation arm, and has a median of 10 years' follow-up. Importantly, the endpoints of overall survival and prostate cancer specific survival were actually the same for all 3 arms, and were quite high. A little more than half of the patients who were on surveillance ended up getting delayed radical therapy of some kind within 10 years.

There was, however, a difference in metastasis-free survival and clinical progression, which were both higher in the active surveillance arm as compared to the treatment arms. Progression to metastatic disease was more than twice as high in the active surveillance arm than the other 2. Most of the patients who had progressed on the active surveillance arm were Gleason 7, and probably were not ideal candidates for active surveillance by today's standards and would not normally be recommended active surveillance.

ANDROGEN DEPRIVATION THERAPIES

Dr. Houranieh. Androgen deprivation therapy plays a large role in prostate cancer management and is used in several areas of prostate cancer care. Androgen deprivation therapy can given be before, during or after radiation or alone in the metastatic setting. It's also continued along with chemotherapy in the more advanced stages. It's use is generally guided by our urologists and the duration of therapy is determined by the risk and stage of the cancer. It can be used for as little as a few months for lower risk, early stage disease or

for a few years for higher risk disease. It can also be continued indefinitely for metastatic disease. Androgen deprivation therapy is a combination of 2 types of therapies, injectable LHRH (luteinizing hormone-releasing hormone) agonists and oral antiandrogens.

A number of products are available. The most commonly used LHRH agonist, at least at the Lexington VAMC in Kentucky, is leuprolide, which comes either in an intramuscular or subcutaneous formulation and can be given at different frequencies either monthly, every 3 months, or every 6 months.

There are also a number of antiandrogens available on the market. The most commonly used one is bicalutamide. It is generally the best tolerated and given once daily, as opposed to the other 2, which are either given twice or 3 times daily.

Dr. Nickols. We typically add ADT to radiation for patients with high-risk prostate cancer, defined as any of the following: A PSA ≥ 20, clinical T3 or higher disease, or Gleason score of ≥ 8. The addition of ADT to radiation in high-risk patients improves overall survival, prostate cancer survival, and biochemical recurrence-free survival. The backbone of this hormone therapy is usually a GnRH analogue like leuprolide.

The data are extensive, including many large phase 3 randomized trials of patients with high-risk prostate cancer treated with radiation plus or minus androgen suppression. Many of these trials were led by the big cooperative trial groups: the Radiation Therapy Oncology Group (RTOG), the European Organisation for Research and Treatment of Cancer (EORTC), and others. Looking at all of the data, the answer to the general question of whether hormone therapy is beneficial is *yes*. The unknown question is what is the optimal duration for this concurrent and adjuvant hormone therapy. The optimal duration is probably somewhere between 1 and 3 years. That's a large range, and clearly preferences of the patient and the comorbidities play a role in the decision of duration. The radiation doses were considerably lower than what is considered standard of care at this time in the trials that have established the use of concurrent and adjuvant hormone therapy with radiation, which needs to be taken in context.

For patients with localized intermediate-risk prostate cancer, a shorter course of hormone therapy is reasonable. The RTOG 9408 and DFCI 95096 trials showed that a 4- to 6-month course of ADT with RT in mostly intermediate-risk patients was better than RT alone. However, studies looking at the different comorbidities present in these patients showed that patients with less comorbidity actually benefit more from the addition of hormone therapy, which needs to be taken into account.

The benefit to the intermediate-risk patients is probably driven by the patients with unfavorable intermediate-risk disease, for example, with the primary Gleason 4 patterns, such as Gleason 4+3 patients rather than Gleason 3+4, patients with higher volume of prostate cancer, patients with multiple intermediate-risk features, etc. For the truly favorable intermediate-risk patients, low-volume disease, low PSA, and Gleason 3+4 pattern, the added value of concurrent ADT may be small.

The mechanism of why ADT may contribute to radiation efficacy may be explained by direct radio-sensitization: the transcription factor androgen receptor activates expression of many genes involved in DNA repair. Interfere with that, and you sensitize to radiation.

Dr. Graff. Of note, we don't use ADT as the primary treatment for localized prostate cancer. This is for use in combination with radiation, in people with positive lymph nodes after surgery and in people with incurable prostate cancer.

Dr. Nickols. The question of whether or not to treat patients with localized high-risk prostate cancer with hormone therapy alone has been answered: The SPCG-7 and NCIC CTG PR3/MRC PR07 trials proved that adding radiation to long-term ADT improved survival in these patients.

The DFCI 95096 trial also showed that patients with a high level of comorbidities benefitted the least from concurrent hormone therapy; cardiovascular risks from the hormone therapy can offset the anticancer effect in these patients.

Analyses of the large randomized trials of radiation with or without hormones looking at the question of whether or not there was increased cardiovascular mortality in the patients that had hormone therapy did not show more cardiovascular mortality. Importantly, those trials were not enriched for patients with comorbidities that would set them up for this risk. One needs to weigh the benefits of adding hormones to radiation against the risks on a patient-to-patient basis.

Dr. Aronson. Another scenario where we used ADT is for patients whose cancer progressed after

primary therapy; for example, when radical prostatectomy and RT are not successful for a patient. We see patients on a regular basis with a rising PSA after primary therapy. Our main goal is to avoid giving ADT to these patients as long as possible and only use it when it is clearly indicated.

The best measure that we typically use is the PSA doubling time. If the PSA doubling time, for example, is > 1 year, than we feel more confident in holding off on starting ADT and instead just monitoring the PSA. Adverse effects (AEs) of ADT are dramatic. We know that patients can get significant fatigue, gain weight, lose muscle mass, have an increased risk of diabetes mellitus, get hot flashes, and develop impotence and loss of libido. And now there are emerging data on an increased risk of Alzheimer disease. We use ADT but only when clearly indicated.

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When I start patients on ADT, in addition to explaining the AEs, I also strongly suggest that, if their health allows, they walk at a brisk rate for at least 30 minutes daily and get on a regular weight training or a resistance training program to try to maintain muscle mass. They need to watch their diet more carefully because they are at increased risk for weight gain. And if they also can do balancing exercises, that would also be ideal. Typically, we also start patients on calcium and vitamin D as there is a risk for bone loss and osteoporosis, and we monitor their bone density.

Dr. Nickols. There's another role for ADT. In patients who have a PSA recurrence after surgery, RT directed to the prostate bed and/or pelvic nodes is a potential curative therapy. There's now some emerging evidence that analogous to the definitive radiation setting, the addition of hormone therapy to salvage radiation may be of value.

There were 2 recent trials published. The RTOG-9601 trial showed a benefit to the addition of bicalutamide for patients who had rising PSA after a surgery and were randomized to radiation that was directed to the prostate bed plus or minus 2 years of bicalutamide. The second trial, GETUG-AFU 16, was similar except that in this case the hormone therapy used was 6 months of the GnRH analogue leuprolide. The RTOG-9601 trial had positive outcomes in multiple endpoints, including survival. The GETUG trial is not as mature but had a biochemical improvement.

I don't think the interpretation of this should be to use hormones with salvage radiation all the time. Importantly, in the RTOG 9601 trial, the patients that had the greatest benefit to the addition of concurrent hormone therapy were those that had a PSA of higher than 0.5 or 0.7. Most patients who get salvage radiation now get it at a much lower PSA, so we probably don't want to overinterpret that data. And, of course, we have to wait for the GETUG-AFU data to mature more to see if there's any hard clinical endpoints met there. Notably, the incidence of gynecomastia in the bicalutamide arm of RTOG 9601 was near 70%. I discuss the addition of hormones with my patients who are getting salvage radiation and usually recommend it to the ones who have the high-risk features, those who would have gotten the concurrent hormones in the definitive setting, those with a PSA greater than 0.5 at the time of salvage, and those with a rapid PSA doubling time.

Dr. Houranieh. Androgen deprivation therapy includes use of LHRH agonists, like leuprolide and antiandrogens like bicalutamide. Some of the short-term AEs from androgen deprivation that we counsel patients on are things like tumor flare, hot flashes, erectile dysfunction, and injection site reactions. Some of the more long-term complications that we touch upon are osteoporosis, obesity, insulin resistance, increased risk of diabetes mellitus and cardiovascular events. We counsel patients on these adverse reactions and do our best with monitoring and prevention.

Dr. Nickols. The ProtecT trial also had some valuable patient-reported outcomes that were very carefully tracked. It confirmed what we already believe. The patients that had primary RT had the greatest negative impact on bowel function and on urinary irritative and obstructive symptoms. The patients who had surgery had the greatest negative impact on sexual function and on urinary incontinence. Obviously, active surveillance had the benefit of avoiding or postponing AEs of local therapy.

You can break up RT for localized disease, into 2 general approaches. The first is external beam radiation. This can be delivered as intensity-

modulated radiotherapy (IMRT), which is the most common approach right now, typically stretched over more than 2 months of daily treatments. In addition, there is a newer technique called stereotactic body radiation therapy (SBRT), which has been applied to localized prostate cancer now for more than a decade. It's efficacy was demonstrated first in low-risk patients as normally is the case. It has the advantage of convenience; it is just 5 treatment days total, which can be accomplished in a couple of weeks. And its convenient for patients who are commuting some distance. That's really important for veterans, as radiotherapy is not available at all VAs.

At the West LA VAMC, we offer SBRT as a standard treatment for men with low and favorable intermediate risk prostate cancer. In addition, we offer it in the context of a clinical trial for patients with unfavorable intermediate- and high-risk prostate cancer.

The other type of radiation therapy is brachytherapy in which the radiation is temporarily or permanently inserted into the target, the prostate. It is a good stand-alone option for men with low- or intermediate-risk prostate cancer. It has the advantage of being relatively fast in that it is done in a day, although it is more invasive than IMRT or SBRT, and certain anatomic features of the prostate and the patient's baseline urinary function can limit its appropriateness in some patients.

There are some recent data of interest for the combination of brachytherapy and external-beam radiation therapy (EBRT). The recently reported ASCENDE-RT trial randomized mostly high-risk patients to either EBRT with 1 year of androgen suppression or EBRT with a boost of brachytherapy to the prostate and 1 year of ADT.

The arm that got the brachytherapy boost actually had half the biochemical recurrence of the EBRT alone but had double the rate of grade 2 acute genitourinary toxicity and triple the rate of grade 3. Metastasis-free survival and other hard clinical endpoints will need longer follow-up, but the biochemical control was quite high: It was about 80% at 10 years out.

Dr. Aronson. For surgical approaches, many VAs now have the da Vinci robot system (Sunnyvale, CA). When we look at the key results, which examine cancer care and AEs, such as incontinence and impotence, there actually is no clear advantage over the open procedure that we previously used. That being said, with the robotic surgery, because we do it laparoscopically, there's significantly less blood loss. The magnification is such that it is much easier to do the surgery. It's also much easier on the surgeon's body, given that you're in an anatomically, ergonomically good position, and patients go home much sooner, typically on postoperative day 1 or postoperative day 2 with less morbidity following the procedure and a much quicker recovery.

PRECISION MEDICINE

Dr. Graff. Prostate cancer may not be cured, even after the best attempts at surgery or radiation. The medical oncologist is probably most utilized with people with incurable prostate cancer. Once it's incurable, it develops tumors in the bones and lymph nodes most commonly, and we call it metastatic prostate cancer.

Right now we use mostly a once-size-fits-all approach. Everyone initially gets some form of castration therapy, usually medical castration with LHRH agonists. However, prostate cancer invariably becomes resistant to those maneuvers. We call that castration-resistant prostate cancer. That opens the door to 6 other treatments that can prolong survival in prostate cancer. Two of the treatments are hormonal (enzalutamide and abiraterone), 2 are chemotherapy (docetaxel and cabazitaxel), 1 is IV radiation with radium-223, and 1 is an immunotherapy (sipuleucel-T).

At this point, there's not a lot of guidance about what to use when except that each of these therapies has unique AEs, so we may not use one of the therapies because it causes a lot of fatigue or it could cause seizures, for example, in a patient at risk for those. Sometimes the therapies are inappropriate. For example, with radium, you wouldn't give it to a patient with a tumor in the liver.

We don't have readily available companion diagnostics to help us narrow the selection. In 2015, there was an article in *Cell* that looked at men with metastatic castration-resistant prostate cancer. The tumors were biopsied and analyzed, and we found some surprising things, including certain mutations called DNA repair defects that could make them susceptible to a drug already approved in ovarian cancer, such as olaparib and rucaparib.

A subsequent study in the *New England Journal of Medicine* looked at patients with advanced prostate cancer whose cancers have these DNA repair defects. Those cancers were susceptible

BIBLIOGRAPHY

American Urological Association. Prostate cancer community responds to new recommendation for prostate cancer testing [press release]. http://auanet.mediaroom.com/2017-04-17-Prostate-Cancer-Community-Responds-To-New-Recommendation-For-Prostate-Cancer-Testing. Published April 17, 2017. Accessed April 24, 2017.

United States Preventive Services Task Force. Prostate cancer screening draft recommendations. https://screeningforprostatecancer.org/read-the-materials/. Published 2017. Accessed April 27, 2017.

Hu JC, Nguyen P, Mao J, et al. Increase in prostate cancer distant metastases at diagnosis in the United States. *JAMA Oncol.* 2016. [epub ahead of print]

Graff JN, Baciarello G, Armstrong AJ, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naïve metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol.* 2016;27(2):286-294.

Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med.* 2016;375(15):1415-1424.

Brundage M, Sydes MR, Parulekar WR, et al. Impact of radiotherapy when added to androgen-deprivation therapy for locally advanced prostate cancer: long-term quality-of-life outcomes from the NCIC CTG PR3/MRC PR07 randomized trial. *J Clin Oncol.* 2015;33(19):2151-2157.

Mason MD, Parulekar WR, Sydes MR, et al. Final report of the Intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol.* 2015;33(19):2143-2150.

Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med.* 2015;373(18):1697-1708.

Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell.* 2015;161(5):1215-1228.

Sweeney CJ, Chen Y, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med.* 2015;373(8):737-746.

Graff JN, Puri S, Bifulco CB, Fox BA, Beer TM. Sustained complete response to CTLA-4 blockade in a patient with metastatic, castration-resistant prostate cancer. *Cancer Immunol Res.* 2014;2(5):399-403.

Graff JN, Drake CG, Beer TM. Complete biochemical (prostate-specific antigen) response to sipuleucel-T with enzalutamide in castration-resistant prostate cancer: a case report with implications for future research. *Urology.* 2013;81(2):381-383.

King CR, Freeman D, Kaplan I. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol.* 2013;109(2):217-221.

Schröder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. Screening and prostate cancer mortality in a randomized European study. *N Engl J Med.* 2009;360(13):1320-1328.

Shelley MD, Kumar S, Coles B, Wilt T, Staffurth J, Mason MD. Adjuvant hormone therapy for localized and locally advanced prostate carcinoma: a systematic review and meta-analysis of randomized trials. *Cancer Treat Rev.* 2009;35(7):540-546.

Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol.* 2006;24(27):4448-4456.

to the PARP (poly ADP ribose polymerase) inhibitor olaparib. That's an example of where looking and sequencing a tumor could lead to a treatment selection. The PARP inhibitors are not yet approved in prostate cancer, but the Prostate Cancer Foundation is interested in supporting research that could help deliver appropriate therapies to veterans in particular whose cancers have certain markers.

So, we are biopsying patients' tumors, looking at the mutations in their germline DNA, and matching patients to treatments and vice versa. The DNA repair defects is the one that's probably under most active evaluation right now. Another example of a biomarker is the AR-V7, which is a mutation in the androgen receptor that renders the cancer resistant to enzalutamide and abiraterone.

Also, I have a study of pembrolizumab which is a PD-1 inhibitor, and I've seen some very good responses to that therapy. And we're not yet sure how to identify prospectively those patients who are likely to respond.

USE OF IMAGING

Dr. Nickols. The sensitivity of technetium-99m bone scans and CT (computed tomography) scans is not good enough. Many patients that we classify as M0, but with clear evidence of disease with a rising PSA, will be more accurately classified as M1 when the imaging allows this to be the case.

I think prostate-specific membrane antigen positron emission tomography (PET), which is not approved at this time, is going to be of value. A lot of data are coming out of Europe and in the recurrence setting show that PET imaging can detect metastatic sites at PSA values as low as 0.2 with the per lesion sensitivity around 80% and a specificity upward of 97%. This is clearly far and away much better than anything we have now.

There's going to be a whole cohort of patients that we literally can't see now, patients with essentially minimally metastatic disease, and they will be revealed when the imaging gets there. And the question is what to do for these patients. Treating patients with a heavy metastatic disease burden is much different from treating patients who may have just one or a few areas of disease outside of their prostate. And we need new strategies for these patients. We are now looking at new treatment regimens for patients with limited metastatic disease burden. I think this is going to be important going forward.

It's also worth asking: What is the role of local therapy in patients with advanced prostate cancer, patients with metastatic disease? If you look at the patients who were in a lot of the old trials, for example, the NCIC trial, that was adding radiation to hormone therapy for high-risk patients,

about 25% of patients in that trial had a PSA > 50. That's a lot. Many of those patients probably had occult metastases. And there are trials now looking at the role of local therapy in metastatic patients.

Another area of interest is precision oncology, which Dr. Graff touched on, is starting to play a big role in the metastatic setting, but what about the local setting? There are now genomic classifiers available to help with risk assessments, but we don't yet have much in the way of predictive tools that help guide specific therapies in the localized setting. We know that patients, for example, who have germline BRCA1 or 2 mutations have a worse outcome, period, after local therapy; and right now it may play some into treatment decisions, but we don't have tailored therapy yet in the localized setting at the molecular level. And I think this is something that we need to start looking at.

Dr. Aronson. The VA is a very rich environment for performing clinical research as well as translational research (bench to bedside). And for example, at the West Los Angeles VAMC, I think one of the key steps that we have taken, moving forward is now our urology, radiation oncology, and hematology-oncology research groups have now merged together. This allows us to not only combine our administrative resources but to really improve the ability for us to perform high-quality research in our veterans. And so that's a model which I think other VAs might consider pursuing, depending upon their circumstances.

AUTHOR DISCLOSURES

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