Informed Prostate Cancer Support Group Inc.
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Sunday, October 18,

October 2020 NEWSLETTER

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Volume 13 Issue 10

- **Saturday, October 17th, 2020 IPCSG - Live-Stream Event, 10:00am PT**
- Dr.Carl Rossi and Dr. John Einck "Advances in Proton Therapy"
  - Carl Rossi, MD, radiation oncologist and Medical Director of the California Proton Treatment Center has personally treated more than 10,000 prostate cancer patients with proton radiation over the last 26 years—more than any other physician in the world.
  - John P. Einck, MD, Radiation Oncologist and Professor of Radiation Medicine and Applied Sciences believes in a team-based approach to patient care. Dr. Einck joined California Protons Treatment Center shortly after the center's opening in 2014. His treatment philosophy emphasizes patient education and encourages everyone to participate in deciding what course of treatment is best for them and their personal goals.
- Due to COVID-19, no in-person meetings at the Sanford Burnham Prebys Medical Discovery Institute will take place until further notice. This meeting will be live-streamed and will also be available on DVD.
- **For further Reading: https://ipcsg.blogspot.com/**
- **For Comments, Ideas and Questions,** email to Newsletter@ipcsg.org

September 2020 Informed Prostate Cancer Support Group Online Presentation

Developments in Immunotherapy in Prostate Cancer

Summary by Bill Lewis

Dr. Sumit Subudhi, Assistant Professor, Genitourinary Medical Oncology, MD Anderson Cancer Center

1. What is the Prostate? It's an organ found only in men. Its function is to liquefy ejaculation fluid. It is primarily known for the problems associated with it: Infection (prostatitis), urinary symptoms (e.g., weak flow due to "BPH" – prostate enlargement), and cancer. There are about 240,000 new cases of prostate cancer annually; about twice as many as new cases of lung cancer in men. But deaths from prostate cancer are far fewer (about 30.000) vs. lung cancer (about 90,000). So most men with prostate cancer die of something else, whereas most with lung cancer die from it. Risk factors for prostate cancer include "unmodifiable" factors – age, race and family history / genetic factors – as well as a major modifiable risk factor, which is diet (poor diet leading to a "beer belly" shape and overweight), along with exercise. Dr. Subudhi is not a fan of supplements, but rather of healthy eating and exercise.

2. What are Symptoms of Prostate Cancer?

Painful or burning urination, Inability to urinate or difficulty in starting to urinate, Difficulty trying to hold back urination, Weak or interrupted urine flow, Frequent or urgent need to urinate, Trouble emptying the bladder completely, Blood in the urine or semen, Difficulty having an erection, and/or Continual

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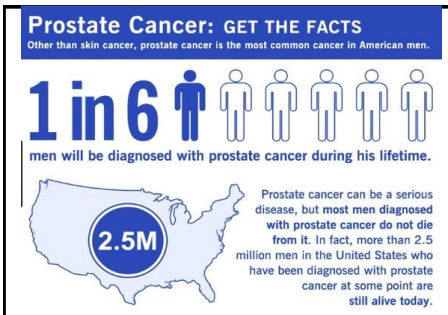

Organization

a 501c3 non-profit organization - all positions are performed gratis

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NEWSLETTER
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PROSTATE CANCER—*2 WORDS, NOT A SENTENCE*

What We Are About

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCa are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

Meeting Video DVD's

DVD's of our meetings are usually available in our library for $10ea. Refer to the index available in the library. They can also be purchased through our website: http://ipcsg.org Click on the 'Purchase DVDs" tab. However since this meeting was not recorded at the speakers request, only the slides will be available for download.

The DVD of each meeting is available by the next meeting date.

From the Editor

Due to COVID-19 no in-person meetings will be held until further notice. We will continue to post and distribute the newsletter in the interim. Our speaker this month will be streamed and broadcast via the group web site. In order to include more articles of interest in this issue, we have included extra pages in the web distributed version of the newsletter. The mail version is limited to ten pages.

Articles of Interest

- Spine metastasis in patients with prostate cancer: Survival prognosis assessment
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- Giri and Gomella on Fostering a New Framework for Genetic PCa Testing Guidelines
- New online model identifies which men can have fewer biopsies on active surveillance

Join the IPCSG TEAM

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Lyle LaRosh @ 619-892-3888; or **Director** Gene Van Vleet @ 619-890-8447.

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pain in the lower back, pelvis, hips or thighs.

3. What Tests are Used to Screen for Prostate Cancer? A "digital rectal exam" (DRE), and the prostate-specific antigen (PSA) blood test. Although 4.0 ng/ml is the traditional cut off, there is truly no "normal" value. When the PSA is between 4 and 10, about 30-40% of those who choose to have a biopsy are found to have prostate cancer. PSA is made by both malignant AND benign prostate cells.

4. What Affects PSA Blood Test Results? Higher PSA levels may be due to an enlarged prostate, age, infection, ejaculation, bicycling (he nevertheless encourages bike riding as good exercise), horseback riding, or cancer. Lower levels may occur due to medications herbal products (the use of which should be disclosed to the doctor, so that their effect can be taken into account) or obesity.

5. What is a Gleason Pattern/Score? It is an assessment of the abnormality of the cells seen in biopsy tissue, ranked from 1 to 5. The aggressiveness of the cancer has been correlated with the degree of abnormality. The most common "pattern" (1 to 5) is added to the number for the second-most common pattern, to yield a score from 2 to 10. Scores from 2 to 6 are considered low risk cancer – with little or no risk of spreading. Scores from 8 to 10 are considered high risk. It is the spreading of the cancer that is likely to lead to a shorter lifespan.

6. What Doctors are Involved in Prostate Cancer? The "primary care" doctor (a generalist), a urologist (who does prostate surgery), a radiation oncologist (does radiation), a medical oncologist (often involved when metastases are found), a pathologist (looks at biopsy tissue samples) and a radiologist (interprets scans such as CT scans, bone scans and MRI's).

7. Why Immunotherapy? The immune system can eradicate tumor cells. It has adaptability, specificity, and (most importantly) memory. In some cases, the cancer can be cured by the immune system. Historical examples include "Coley's toxin" used starting in 1891, which cured 20% of the ~100 men Dr. William Coley, and contained a tumor necrosis factor obtained from a streptococcus strain. However, radiation therapy was found to be more effective, so Coley's work was not followed up on. In the 1950's, bone marrow transplantations were initiated, and found effective for many cancers (such as leukemias and lymphomas) – though not for prostate cancer.

When prostate cancer is diagnosed, this means that the cancer has "evaded" the immune system and grown large enough to be detected. In immunosuppressed patients (such as those on drugs to prevent rejection of a transplanted organ), many more cases of cancer of various types – including prostate cancer – are found, vs. other patients.

8. How Can We "Improve the Tumor Microenvironment"? There are actually a number of immune system cells that promote cancer growth! Others fight it. The object of immunotherapy is to shift the balance toward more of the immune cells that fight the cancer. This can potentially be done through bacterial stimulants (as in Dr. Coley's toxin), cytokines (such as interleukin-2, which hasn't lived up to its initial hype), vaccines (such as Provenge (sipuleucel-T), which is made from a patient's own immune cells, and provides a modest average survival gain in patients with metastatic, castrate-resistant prostate cancer), or targeting immune checkpoints.

9. What is our New Understanding of T Cell Regulation, by Positive & Negative Signals? The T cells have a receptor (TCR) protein that can attach to cancer cells – but it doesn't cause the T cell to proliferate (i.e., bring more T cells to attack the cancer). A second receptor on the T cell, called CD28, if activated by binding to an antigen presenting cell (APC, i.e., a dendritic cell or macrophage) does cause (desirable) T cell proliferation. That's the positive signal. Attenuation of T cell activity (negative signal) is provided by another protein of the T cell binding to a site on the APC. These attenuating receptors are called immune checkpoints, and three have so far been found. These tell the immune system T cells to slow down / stop attacking the cancer (or any other infection). One such checkpoint protein is CTLA-4. It limits proliferation of T cells. Yervoy (Ipilimumab) acts against this, so T cell activity is able to proceed. Yervoy has shown life prolongation in melanoma patients, and almost

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20% of the patients had long-term survival. PD-1 and PD-L1 are also "brakes" on the immune system. They similarly limit the responses of the T cells.

10. What are the Challenges/Limitations of Immune Checkpoint Therapies? Only a subset of patients benefit. There are toxicities: "immune-related adverse events." And measuring the disease burden / treatment response is difficult. However, immune-related response criteria have been developed.

The toxicities can affect any part of the body. However, the most common are skin rashes and gastrointestinal problems (bloody diarrhea!). Less commonly, it can affect the lungs (shortness of breath) or the brain (fatigue).

11. What About a Cure Instead of Merely Prolonging Life a Little? In Dr. Subudhi's practice, one patient with melanoma facing hospice had one dose of Yervoy, and initially his tumor grew (so he went on hospice), but then the cancer disappeared completely! Such a one-dose cure is rare. But almost 20% of treated melanoma patients live a lot longer than those not on Yervoy. Now, research is directed toward improving survival with combinations of immunotherapies. Yervoy (anti-CTLA-4) plus Nivolumab (anti-PD-1) gave a great prolongation of life for 58% of melanoma patients.

The FDA has now approved a great variety of checkpoint inhibitors for various cancers, but not yet any for prostate cancer.

12. Do Immune Checkpoint Therapies Work in Prostate Cancer Patients? So far, the answer is mainly, "No." Neither anti-PD-1 nor anti-CTLA-4 gave a survival benefit, except perhaps for a subset of patients with metastatic prostate cancer who were treated after chemotherapy, with anti-CTLA-4.

13. Can We Identify the Subset of Patients with Metastatic Prostate Cancer Who Benefit from Anti-CTLA-4? Thirty patients gave tissue samples before treatment with four doses of Yervoy. It was found that patients who started with more immune system T cells got much better results from the immunotherapy.

14. What's Different Between Prostate Cancer and Melanoma Following Treatment with Yervoy? In prostate cancer, two types of immunosuppressive macrophages appear (PD-L1 CD68 cells and Vista CD68 cells) – because the cancer is getting smart -- but not in melanoma.

15. Can We Improve on the Clinical Responses to anti-CTLA-4? Combining both types of drugs (anti-CTLA-4 along with anti-PD-1/anti-PD-L1) gave benefit to about 25% of pre-chemo mCRPC (metastatic castrate-resistant prostate cancer) men, and to about 10% of post-chemo mCRPC men. These aren't great results, but they are the best seen so far. There is a need to explore the dosing and schedule of doses to try to mitigate toxicities (i.e., side effects). New combinations will be needed to provide clinical benefit for a greater number of patients.

16. What About the Immunosuppressive Prostate Bone Tumor Microenvironment? In a statistical study of 10,000 men, about 70% of men with metastatic prostate cancer have it in the bones, or in the bones and in the lymph nodes. Compared with men having only lymph node metastases, these men lived only 21 months, vs. about 32 months (with Taxotere chemotherapy in each case). The cancer cells in the bones are very deficient in T cells compared to other nearby cells, and the primary tumor cells are somewhat deficient, but not so much as the bone metastases. So whereas immune checkpoint monotherapies (e.g., Yervoy) have low efficacy generally in prostate cancer patients, this is especially so for those with predominantly bone metastases. But recently, cytokines called TGF-β1 were found to be elevated in prostate cancer cells in mouse bones, and a combination of Yervoy and an anti-TGF-β1 drug improved survival – so human trials are planned. This holds promise for improved outcomes for patients with a lot of bone metastases.

17. What Can We Expect Moving Forward? There will be efforts to increase T cell infiltration into prostate cancer cells (where they are now deficient). Immune checkpoints will continue to be targeted. Many more checkpoints than the three discussed above have been identified already. The following figure shows some additional immunotherapy targets:

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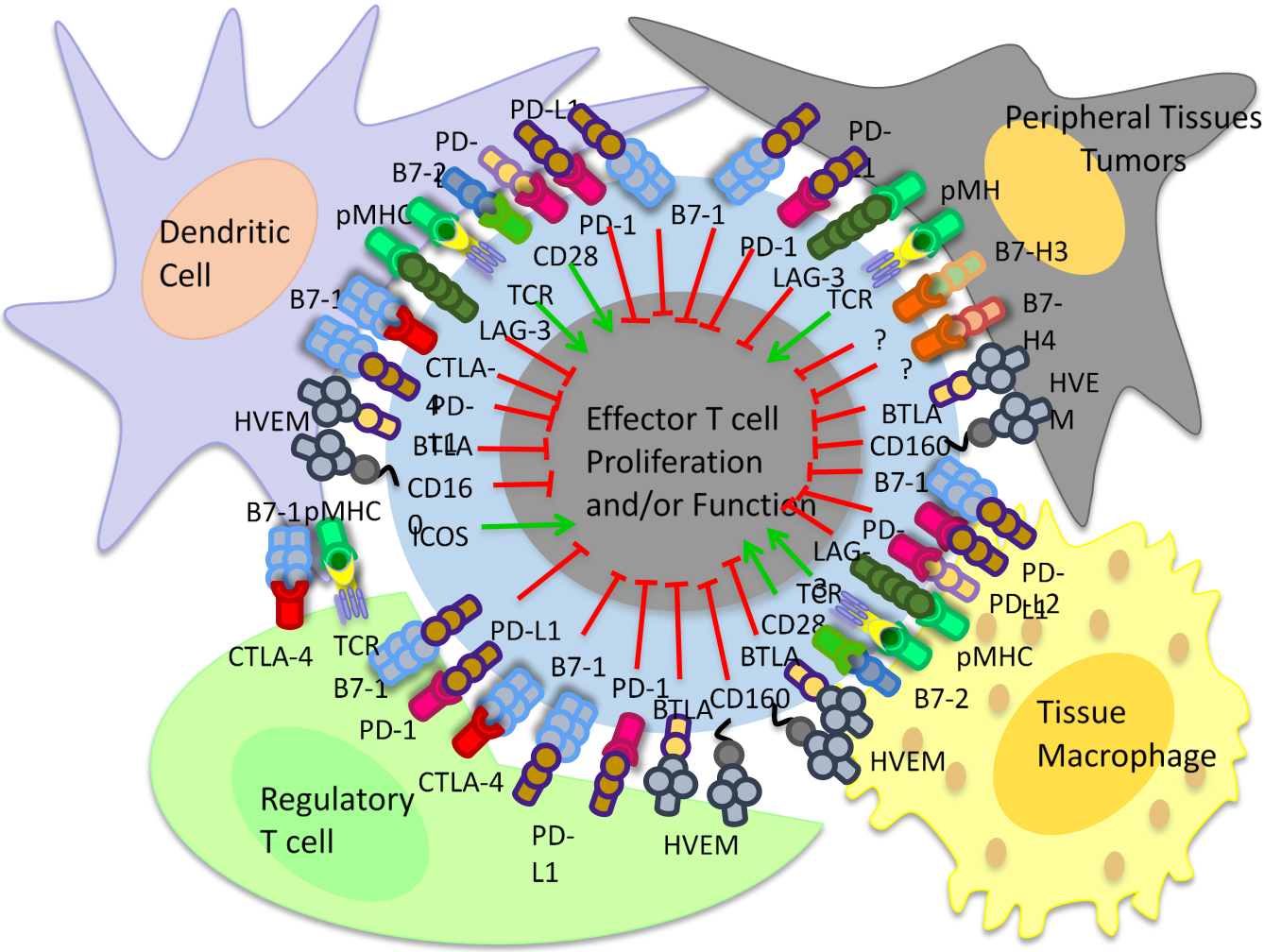

Efforts will be made to target immunosuppressive cells (e.g., certain macrophages). And the roles and possible influencing of other factors will be studied, including metabolism, hypoxia, epigenetics, the microbiome, etc. There will also be efforts to better identify which patients will benefit from the new protocols.

Questions

What about CAR-T cell therapy? It's effective and FDA-approved in lymphoma, a blood-based cancer, but is still a few years away in solid tumors such as prostate cancer. Clinical trials have started.

What about CRISPR, where UPenn has been studying T cells with 3 genes interfering with effectiveness deleted, and an inserted gene that gives the cells a claw-like protein for finding specific receptors on cancer cells? Their 2019 publication showed the process was safe. Do you see application in prostate cancer soon? Dr. Subudhi believes that CRISPR technology is not ready yet for use alone.

What about the apparent crossover of survival graph lines after 5 years for Provenge vs. placebo? There are hardly any patients still alive at that point, so the graph becomes statistically meaningless. That's why clinical trials focus on the point where 50% of patients are alive, and compare the time at which the test arm and the control arm of the study reach that status.

What indicators do you focus on in treating patients? Dr. Subudhi uses patient symptom reports, PSA, and scans of various types.

What immunotherapies are available now? Only Provenge; all others are only available in clinical trials.

As a patient, how do you know if Provenge is working for you? It doesn't keep the PSA from go-

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ing up, and it doesn't keep the cancer from growing, but a survival benefit has been shown, so we have to conclude that the cancer grows more slowly because of the treatment.

Do you control for gut microbiome in your human studies? Still thinking about doing that. People on probiotics and those who recently had antibiotics actually did not do as well in melanoma checkpoint inhibitor studies, so we know there are effects. In Oregon, fecal transplants from patients who did well from checkpoint inhibitor treatment, to other patients are being studied.

What about cryoablation and inter-tumoral injection of checkpoint inhibitors? Sounds great in theory, but not working out well in practice.

What about Provenge for a patient with prostate cancer only in the prostate? Hasn't seemed to help high-risk patients, but it is now being tested in men on active surveillance.

In what order should treatments be given? Does chemo after Provenge destroy its effects? Dr. Subudhi says that Provenge produces memory cells that are not destroyed by chemo. He likes to give Provenge first. The lower the PSA, the more Provenge seems to help. But if a patient has a very active cancer / painful symptoms, he goes right to chemo. Immunotherapy (except for Provenge) is only given in clinical trials, and those open and close fairly frequently, so you have to watch for opportunities.

CD8 T cells seem to decrease in older men. Is this a reason why immunotherapy is less effective in older men? This seems to be a factor, though the correlation does not always hold true. There are ways of boosting the immune system, including CAR-T cells and the use of CRISPR technology that hold promise for the future.

What about getting immunotherapy when biochemical recurrence shows up 15 years after surgery, radiation and chemo? There's a study at Columbia University called Magic-8 that addresses that situation. If the PSA is rising, but the tumors aren't yet otherwise detectable, Dr. Subudhi would tend to watch it, and put off the side effects of hormone treatment or immunotherapy until a decision point is reached. A decision point might be when the PSA doubling time is 3-6 months. See "PSA doubling time calculator" online.

How to reach him? sksubudhi@mdanderson.org Use "IPCSG" in the subject line, because he gets 200 or more emails daily. Normally, he replies within 3 days.

On the Lighter Side

"I blend my conservative sensibilities with my liberal drinking and end up with a pleasantly moderate view."

Denise gets offered the senior discount for the first time.

Articles of Interest

Spine metastasis in patients with prostate cancer: Survival prognosis assessment

onlinelibrary.wiley.com

Aymeric Amelot MD, PhD E-mail address: aymmed@hotmail.fr

http://orcid.org/0000-0003-3659-291X

Abstract

Background - Patients presenting spine metastasis (SpM) from prostate cancer (PC) form a heterogeneous population, through this study, we aimed to clarify and update their prognostic assessment.

Methods - The patient data used in this study was obtained from a French national multicenter database of patients treated for PC with SpM between 2014 and 2017. A total of 72 patients and 365 SpM cases were diagnosed.

Results - The median overall survival time for all patients following the event of SpM was 28.8 months. First, we identified three significant survival prognostic factors of PC patients with SpM: good Eastern Cooperative Oncology Group/World Health Organization personnel status (Status 0 hazard ratio [HR]: 0.031, 95% confidence interval [CI]: 0.008–0.127; p < .0001) or (Status 1 HR: 0.163, 95% CI: 0.068–0.393; p < .0001) and SpM radiotherapy (HR: 2.923, 95% CI: 1.059–8.069; p < .0001). Secondly, the presence of osteolytic lesions of the spine (vs. osteoblastic) was found to represent an independent prognosis factor for longer survival [HR: 0.424, 95% CI: 0.216–0.830; p = .01]. Other factors including the number of SpM, surgery, extraspinal metastasis, synchrone metastasis, metastasis-free survival, and SpM recurrence were not identified as being prognostically relevant to the survival of patients with PC.

Conclusion - Survival and our ability to estimate it in patients presenting PC with SpM have improved significantly. Therefore, we advocate the relevance of updating SpM prognostic scoring algorithms by incorporating data regarding the timeline of PC as well as the presence of osteolytic SpM to conceive treatments that are adapted to each patient.

Breakthrough Device Designation for miR Sentinel™ urine test

prostatecancerinfolink.net

miR Scientific's Sentinel™ Test is the only standalone, non-invasive liquid biopsy urine test that accurately detects, classifies and monitors prostate cancer at the molecular level with 95% Sensitivity and Specificity.

According to a media release issued on Tuesday this week by miR Scientific, the US Food and Drug Administration (FDA) has issued a Breakthrough Device Designation for the company's new urine-based test for risk of prostate cancer (the miR Sentinel™ Prostate Test). The FDA's Breakthrough Device Designation allows for accelerated approval of novel medical devices that have the potential to provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.

We have previously reported on the potential value of this test in the early assessment of categorizable forms of prostate cancer and their risk. We hope to see this product become widely available in the relatively near future for a variety of potential applications in the diagnosis and management of prostate cancer.

prostatecancerinfolink.net

Real-world survival benefit of treatment with sipuleucel-T (Provenge)

[could buy 14-15 months survival]

So there are new, interesting data regarding the treatment of men with metastatic, castration-resistant prostate cancer (mCRPC) with sipuleucel-T (Provenge) as well as either or both of abiraterone acetate (Zytiga) and enzalutamide (Xtandi) — known generically as androgen-receptor signaling pathway inhibitors or ASPIs. However, these data need to be assessed with some caution at this time.

The new data come from an article by McKay et al. in *Advances in Therapy*. The authors report retrospective, observational data from > 6,000 men with advanced prostate cancer in the US who were chemotherapy naive and who had continuous Medicare eligibility (Parts A, B, and D, but not Part C) over a 3-year observation period between 2014 and 2017. The entire text of this article is available on line, and so anyone can read the original article for themselves.

According to McKay et al., their patients all had to have been mCRPC-treatment-naïve men who had had no previous FDA-approved treatment for mCRPC for 12 months before any initial claim (in

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2014) for treatment of mCRPC, with the exception of standard forms of androgen deprivation therapy (ADT). The patients were then all required either to have continuous coverage for 36 months or to have died.

Here is a basic summary of their findings:

- The data set included 6,044 eligible men with mCRPC of similar levels of disease severity.
- The average (median) overall survival (OS) for the entire set of 6,044 patients was 23.0 months
- When sipuleucel-T was administered to patients at any time during the 3-year observation period, the median OS was
  - 35.2 months for the 906 patients who received sipuleucel-T and at least one ASPI
  - 20.7 months for the 5,092 patients who received no sipuleucel-T
  - The adjusted hazard ratio (aHR) was 0.59
  - When sipuleucel-T was administered to patients as first-line therapy during the 3-year observation period, the median OS was
  - **34.9 months** for the 647 patients who received sipuleucel-T and at least one ASPI
  - **21.0 months** for the 4,810 patients who received no sipuleucel-T
  - The aHR was 0.56

McKay et al conclude that their analysis suggests:

… use of sipuleucel-T at any time was associated with improved OS compared with ASPI use alone.

However, they are also careful to point out that their analyses

… are intended as descriptive rather than definitive as this dataset contains limited data on key clinical factors.

and that

While selection bias is a risk in secondary claims data, this research provides important insight into real-world treatment outcomes.

The only way to clearly demonstrate whether combined, sequential treatment of men with newly diagnosed mCRPC with sipuleucel-T and an ASPI as opposed to just ASPIs would be through an appropriately constructed, randomized clinical trial. However, whether any company or other funding body would be willing to cover the costs of such a trial (which might require something like1500 patients) is open to question.

The real issue is going to be whether, given the apparent size of the extension of survival times (of about 14 or 15 months) for these patients with mCRPC if they are treated with both sipuleucel-T and an ASPI, someone can justify the cost of such a trial. Should the results of such a trial be positive, however, it might significantly alter the standard of care for men with metastatic disease who become castration-resistant after initial treatment with standard forms of ADT.

The virtual prostate cancer patient

prostatecancerinfolink.net

The virtual prostate cancer patient

Posted on October 15, 2020

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A new type of "educational" service has been brought to our attention that uses virtual reality (VR) systems allowing a number of opportunities for men to "talk" to a virtual prostate cancer patient about their own risks for prostate cancer and things like the risks and benefits of PSA testing.

This new VR system has been developed by the CDC Division of Cancer Prevention and Control in collaboration with the National Association of Chronic Disease Directors and a health simulation company called Kognito.

Here is the link to the "Talk to Nathan" set of VR programs.

Basically the system can be used to do three things:

- It allows a man to"talk" to a virtual human ("Nathan") who has had a prostate cancer "scare" so that the man can start to learn how to ask their own healthcare providers about risk assessment and testing for risk of prostate cancer.
- It allows a man to "talk" to Nathan about his own prostate cancer and what he had learned over his 10-year journey since diagnosis.
- It can also be used to help primary care physicians to learn how best to talk to their patients about the risks and benefits of PSA testing for risk of prostate cancer ("screening").

While we find this type of VR system interesting intellectually, what we would really like is to ***get feedback from real patients*** as to what they think about these systems specifically and whether you think Prostate Cancer International should recommend these systems to men who believe that they may be at risk for prostate cancer and need to get tested for that risk or men who have been recently diagnosed and are just starting to learn about their journey. Try it and give us some feedback by email. https://www.cdc.gov/cancer/prostate/talk-to-nathan/index.html

PSMA, PSMA Imaging and Therapy

https://www.cancerabcs.org/advanced-prostate-cancer-blog/2020/10/12/the-efficacy-of-psma-scans-and-therapy

One of the hottest topics in advanced prostate cancer is prostate -specific membrane antigen (PSMA) scans and PSMA-targeted radionuclide therapy. PSMA is a type II membrane protein expressed in all forms of prostate tissue, including prostate cancer. PSMA sits on the surface of prostate cells and is heavily upregulated in prostate cancer, especially in metastatic and castration-resistant disease, making it a good target for scans and treatments.

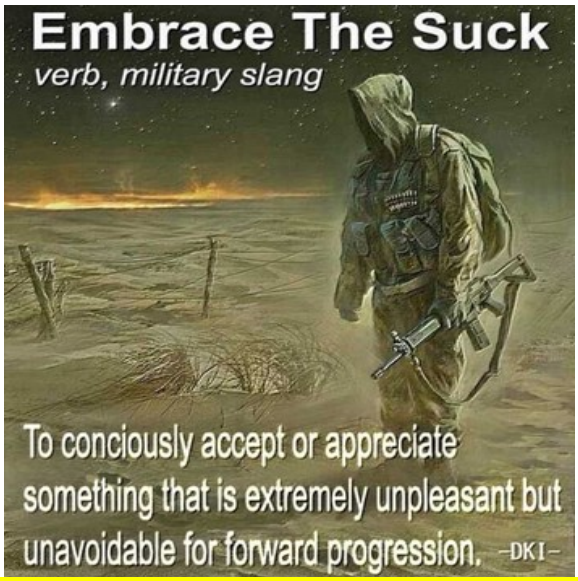
At the 2019 ASCO virtual meeting, abstract 5013 was presented. The abstract described the association of noninvasive, radiographic measurement of prostate-specific membrane antigen (PSMA) expression with the response to PSMA-targeted radionuclide therapy (TRT). PJ Vlachostergios, MJ Niaz, SA Mosallaie, et al.

The study abstract referenced evaluated 216 men with metastatic CRPC who were treated with PSMA-targeted radionuclide therapy. The therapies included: 177Lu-J591 (n = 136), 177Lu-PSMA-617 (n = 38), Lu-J591 + Lu-PSMA-617 (n = 6), 225Ac-J591 (n = 7), and 90Y-J591 (n = 129).

Overall, 53.7% of men received low-dose treatment. By imaging, 74.5% of the subject men had high PSMA expression, which was associated with significantly more frequent PSA decline with the radionuclide therapies. There were 13 men with no PSMA uptake on their scans but still exhibited PSA declines when receiving PSMA target therapy.

In this first study to analyze PSMA-targeted radionuclide therapy response via imaging expression, the results demonstrated that the PSMA expression level is associated with response likelihood. However, negative imaging does not exclude all men who may benefit from PSMA therapy.

On the lighter side



Also Applicable to men with Prostate Cancer for DRE, Biopsy, MRI/CT Scan, and treatment with Surgery, Radiation, ADT, and Chemotherapy.

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NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Lyle LaRosh, and Gene Van Vleet are available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or gene@ipcsg.org to coordinate.

Member and Director, John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: https://ipcsg.org/personal-experience

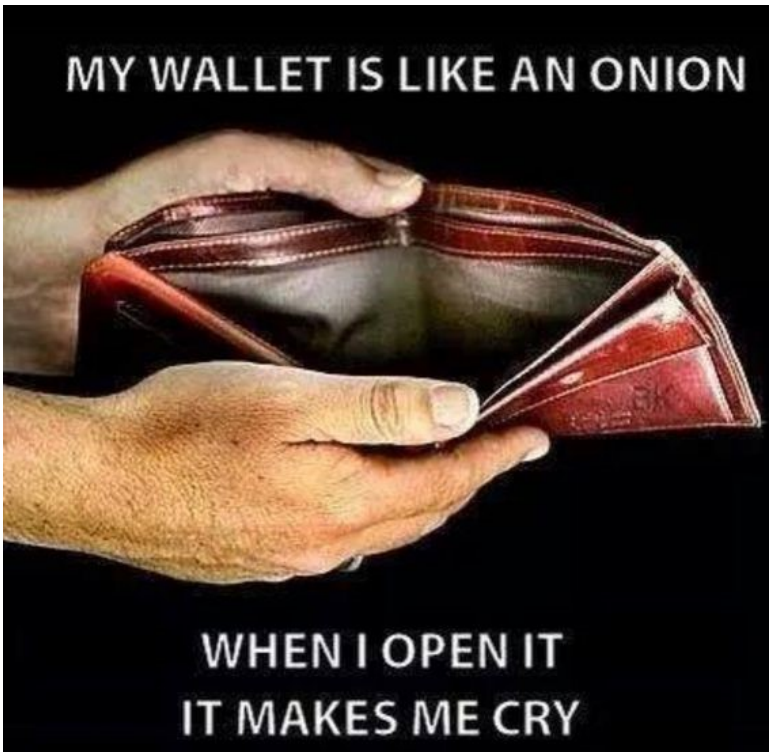
Our brochure provides the group philosophy and explains our goals. Copies may be obtained by mail or email on request. Please pass them along to friends and contacts.

Ads about our Group are in the Union Tribune the week prior to a meeting. Watch for them.

FINANCES

We want to thank those of you who have made special donations to IPCSG. Remember that your gifts are tax deductible because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. Corporate donors are welcome!



While our monthly meetings are suspended, we still have continuing needs, but no monthly collection. If you have the internet you can contribute easily by going to our website, http://ipcsg.org and clicking on "Donate" Follow the instructions on that page. OR just mail a check to: IPCSG, P. O. Box 420142, San Diego CA 92142

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cookwithkathy.wordpress.com

Cerenkov Luminescence Imaging Accurately Identifies Surgical Margin Status During Radical Prostatectomy

https://cookwithkathy.wordpress.com/2020/10/12/cerenkov-luminescence-imaging-accurately-identifies-surgical-margin-status-during-radical-prostatectomy/

A new intraoperative imaging technique, Cerenkov luminescence imaging (CLI), can accurately assess surgical margins during radical prostatectomy, according to a first-in-human research published in the October issue of The Journal of Nuclear Medicine. The feasibility study showed that 68Ga-PSMA CLI can image the entire excised prostate specimen's surface to detect prostate cancer tissue at the resection margin.

Radical prostatectomy is one of the primary treatment options for men with localized prostate cancer. The goal of a radical prostatectomy is to completely resect the prostate without positive surgical margins. Incomplete removal of the cancer tissue during radical prostatectomy is often associated with poorer patient outcomes, including increased likelihood of recurrence and prostate cancer-related mortality.

Prostate-specific membrane antigen (PSMA) ligand positron emission tomography (PET) has emerged as an accurate tool to detect prostate cancer both in primary staging and at time of biochemical recurrence. As PET imaging agents also emit optical photons via a phenomenon called Cerenkov luminescence, researchers sought to evaluate the feasibility and diagnostic accuracy of CLI in detecting prostate cancer.

"Intraoperative radioguidance with CLI may help surgeons in the detection of extracapsular extension, positive surgical margins and lymph node metastases with the aim of increasing surgical precision," stated Christopher Darr, PhD, resident at the Department of Urology of the University Medical Center Essen in Essen, Germany. "The intraoperative use of CLI would allow the examination of the entire prostate surface and provide the surgeon with real-time feedback on the resection margins."

The single-center study included 10 patients with high-risk primary prostate cancer. 68Ga-PSMA PET scans were performed followed by radical prostatectomy and intraoperative CLI of the excised prostate. CLI images were analyzed postoperatively to determine regions of interest based on signal intensity, and tumor-to-background ratios were calculated. CLI tumor margin assessment was performed by analyzing elevated signals at the surface of the intact prostate images. To determine accuracy, tumor margin status as detected by CLI was compared to postoperative histopathology.

Tumor cells were successfully detected on the incised prostate CLI images and confirmed by histopathology. Three patients had positive surgical margins, and in two of the patients, elevated signal levels enabled correct identification on CLI. Overall, 25 out of 35 CLI regions of interest proved to visualize tumor signaling according to standard histopathology.

Boris A. Hadaschik, PhD, director of the Clinic for Urology of the University Medical Center Essen, added, "Radical prostatectomy could achieve significantly higher accuracy and oncological safety, especially in patients with high-risk prostate cancer, through the intraoperative use of radioligands that specifically detect prostate cancer cells. In the future, a targeted resection of lymph node metastases could also be performed in this way. This new imaging combines urologists and nuclear medicine specialists in the local treatment of patients with prostate cancer."

Source: Society of Nuclear Medicine & Molecular Imaging

nejm.org

Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

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Johann de Bono for the PROfound Trial Investigators*

Abstract

Background

We previously reported that olaparib [lynparza] led to significantly longer imaging-based progression-free survival than the physician's choice of enzalutamide or abiraterone among men with metastatic castration-resistant prostate cancer who had qualifying alterations in homologous recombination repair genes and whose disease had progressed during previous treatment with a next-generation hormonal agent. The results of the final analysis of overall survival have not yet been reported.

Methods

In an open-label, phase 3 trial, we randomly assigned patients in a 2:1 ratio to receive olaparib (256 patients) or the physician's choice of enzalutamide or abiraterone plus prednisone as the control therapy (131 patients). Cohort A included 245 patients with at least one alteration in *BRCA1*, *BRCA2*, or *ATM*, and cohort B included 142 patients with at least one alteration in any of the other 12 prespecified genes. Crossover to olaparib was allowed after imaging-based disease progression for patients who met certain criteria. Overall survival in cohort A, a key secondary end point, was analyzed with the use of an alpha-controlled, stratified log-rank test at a data maturity of approximately 60%. The primary and other key secondary end points were reported previously.

Results

The median duration of overall survival in cohort A was 19.1 months with olaparib and 14.7 months with control therapy (hazard ratio for death, 0.69; 95% confidence interval [CI], 0.50 to 0.97; P=0.02). In cohort B, the median duration of overall survival was 14.1 months with olaparib and 11.5 months with control therapy. In the overall population (cohorts A and B), the corresponding durations were 17.3 months and 14.0 months. Overall, 86 of 131 patients (66%) in the control group crossed over to receive olaparib (56 of 83 patients [67%] in cohort A). A sensitivity analysis that adjusted for crossover to olaparib showed hazard ratios for death of 0.42 (95% CI, 0.19 to 0.91) in cohort A, 0.83 (95% CI, 0.11 to 5.98) in cohort B, and 0.55 (95% CI, 0.29 to 1.06) in the overall population.

Conclusions

Among men with metastatic castration-resistant prostate cancer who had tumors with at least one alteration in *BRCA1*, *BRCA2*, or *ATM* and whose disease had progressed during previous treatment with a next-generation hormonal agent, those who were initially assigned to receive olaparib had a significantly longer duration of overall survival than those who were assigned to receive enzalutamide or abiraterone plus prednisone as the control therapy, despite substantial crossover from control therapy to olaparib. (Funded by AstraZeneca and Merck Sharp & Dohme; PROfound ClinicalTrials.gov number, NCT02987543. opens in new tab.)

ro-journal.biomedcentral.com

Phase I/IIa trial of androgen deprivation therapy, external beam radiotherapy, and stereotactic body radiotherapy boost for high-risk prostate cancer (ADEBAR)

Young Seok Kim

Radiation Oncology **volume 15**, Article number: 234 (2020) Cite this article

Abstract

Background

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To evaluate the clinical outcomes of combination of androgen deprivation therapy (ADT), whole pelvic radiotherapy (WPRT), and stereotactic body radiotherapy (SBRT) boost in high-risk prostate cancer patients.

Methods

This prospective phase I/IIa study was conducted between 2016 and 2017. Following WPRT of 44 Gy in 20 fractions, patients were randomized to two boost doses, 18 Gy and 21 Gy, in 3 fractions using the Cyberknife system. Primary endpoints were incidences of acute toxicities and short-term biochemical recurrence-free survival (BCRFS). Secondary endpoints included late toxicities and short-term clinical progression-free survival (CPFS).

Results

A total of 26 patients were enrolled. Twelve patients received a boost dose of 18 Gy, and the rest received 21 Gy. The Median follow-up duration was 35 months. There were no grade ≥ 3 genitourinary (GU) or gastrointestinal (GI) toxicities. Sixty-one and 4% of patients experienced grade 1–2 acute GU and GI toxicities, respectively. There were 12% late grade 1–2 GU toxicities and 8% late grade 1–2 GI toxicities. Patient-reported outcomes of urinary symptoms were aggravated after WPRT and SBRT boost. However, they resolved at 1 month and returned to the baseline level at 4 months. Three-year BCRFS was 88.1%, and CPFS was 92.3%.

Conclusions

The present study protocol demonstrated that the combination of ADT, WPRT, and SBRT boosts for high-risk prostate cancer is safe and feasible, and may reduce total treatment time to 5 weeks. Boost dose of 21 Gy in 3 fractions seems appropriate.

Trial registration

ClinicalTrials.gov, ID; NCT03322020 - Retrospectively registered on 26 October 2017.

Reserve PARP Inhibitors for mCRPC With BRCA Mutations

Neil Osterweil

medscape.com

For men with metastatic castration-resistant prostate cancer (mCRPC), any new therapy that offers the chance of a higher response rate or longer survival compared with the standard of the care would be welcome.

The US Food and Drug Administration (FDA) recently approved two such drugs for use in men with mCRPC: the poly (ADP-ribose) polymerase (PARP) inhibitors rucaparib (Rubraca) and olaparib (LynParza).

Both drugs were approved for use in the treatment of men with advanced prostate cancer with deleterious germline and/or somatic *BRCA* mutations following treatment with androgen receptor–directed therapy and taxane-based chemotherapy.

But there was difference in the wording of the indication that was approved, as noted by Michael T. Schweizer, MD, and colleagues from the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle, Washington, in a recent commentary published in the *Journal of Clinical Oncology*.

Olaparib received wider approval for treatment of "deleterious or suspected deleterious germline or somatic homologous recombination repair gene (*HRR*)–mutated metastatic castration-resistant prostate cancer" with disease progression following therapy with either enzalutamide or abiraterone (Zytiga).

It's the "deleterious or suspected deleterious" part of that indication that has these experts concerned, inasmuch as this may lead to the drug being used injudiciously to treat some patients who might better be treated with other approaches.

"Using standard-of-care PARP inhibitors in those with uncertain or little chance of benefit could mean missing a window of opportunity for more effective

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therapy. This may result in decreased survival and hamper clinical trial enrollment to the very studies that could define the predictive utility of individual genes," they write.

Elaborating in an interview with *Medscape Medical News*, Schweizer said: "The issue is that olaparib has a long list of genes that would make you eligible to receive it, but it's not clear that many of these genes are good biomarkers for response to that drug."

Although the evidence for a response to PARP inhibitors for patients with *BRCA* mutations is fairly strong, there has not been sufficient evidence to date to suggest that responses would be adequate for patients with other *HRR* mutations, he said.

For patients who have "one of the less common *HRR* genes, maybe without high level of evidence that they are really predictive of response, I would still give careful consideration to some of the other drugs that have been around for a while and that we know have a track record of working well for prostate cancer, such as taxane-based chemotherapy," Schweizer commented.

Mark Pomerantz, MD, a geneticist and specialist in genitourinary oncology at the Dana-Farber Cancer Institute in Boston, Massachusetts, who was not involved in the study, told *Medscape Medical News* that Schweizer and colleagues are "exactly right."

sciencedaily.com

Advanced prostate cancer has an unexpected weakness that can be targeted by drugs: Researchers identified that SUCLA2-deficient prostate cancer cells can be selectively treated with thymoquinone

The compound thymoquinone (TQ) selectively kills prostate cancer cells at advanced stages, according to a new study published in *Oncogene*. Led by researchers at Kanazawa University, the study reports that prostate cancer cells with a deletion of the SUCLA2 gene can be therapeutically targeted. SUCLA2-deficient prostate cancers represent a significant fraction of those resistant to hormone therapy or metastatic, and a new therapeutic option for this disease would have immense benefits for patients.

Hormone therapy is often chosen for the treatment of metastatic prostate cancer but nearly half of patients develop resistance to the treatment in as little as 2 years. A mutation in RB1, a tumor suppressor gene that keeps cell growth under control, has been pegged as a particularly strong driver of treatment resistance and predicts poor outcome in patients.

"Mutations in tumor suppressor genes are enough to induce initiation and malignant progression of prostate cancer, but so far we haven't been able to directly target these mutations with drugs to treat prostate cancer," says the lead author Susumu Kohno. "We wanted to find a genetic aberration associated with that of a tumor suppressor gene which we could target therapeutically."

In the genome, SUCLA2 neighbors RB1. An analysis of prostate cancer cells showed that cells with a RB1 deletion were also missing SUCLA2, pairing up the SUCLA2 deletion with the RB1 deletion present in advanced stage prostate cancer. Kohno and colleagues analyzed prostate cancer tissue and found that 11% of cases were missing both SUCLA2 and RB1.

The researchers screened compounds to identify drugs that would selectively kill cells with a SUCLA2 deletion. Out of around 2,000 compounds, TQ emerged as a hit compound. TQ already has known anti-cancer effects and was shown to be safe in a phase I clinical trial. Kohno and colleagues applied the TQ treatment to a mouse model of SUCLA2-deficient prostate cancer and TQ selectively suppressed tumor growth.

"These findings show that TQ treatment could be an effective therapy for treating prostate cancer cells that harbor SUCLA2 deficiency" says the senior author Chiaki Takahashi.

In a search of genetic databases from patients with prostate cancer, the researchers found that the frequency of SUCLA2 loss was almost perfectly aligned with RB1 loss at every disease stage --

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meaning the SUCLA2 deletion could identify people with prostate cancer needing advanced therapy.

Finding this drug-targetable vulnerability opens a crack in the barrier of treatment resistance for prostate cancer. More work needs to be done to improve efficacy of TQ and identify patients that would benefit from this type of treatment, but the compound provides a promising route for new treatment options for advanced prostate cancer.

Story Source:

Materials provided by **Kanazawa University**. *Note: Content may be edited for style and length.*

Bone health effects of androgen-deprivation therapy and androgen receptor inhibitors in patients with nonmetastatic castration-resistant prostate cancer

https://www.nature.com/articles/s41391-020-00296-y?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+pcan%2Frss%2Fcurrent+%28Prostate+Cancer+and+Prostatic+Diseases+-+Issue%29

Theresa Guise

nature.com

Abstract

Background

Osteoporosis is a skeletal disorder characterized by compromised bone strength, resulting in increased fracture risk. Patients with prostate cancer may have multiple risk factors contributing to bone fragility: advanced age, hypogonadism, and long-term use of androgen-deprivation therapy. Despite absence of metastatic disease, patients with nonmetastatic castrate-resistant prostate cancer receiving newer androgen receptor inhibitors can experience decreased bone mineral density. A systematic approach to bone health care has been hampered by a simplistic view that does not account for heterogeneity among prostate cancer patients or treatments they receive. This review aims to raise awareness in oncology and urology communities regarding the complexity of bone health, and to provide a framework for management strategies for patients with nonmetastatic castrate-resistant prostate cancer receiving androgen receptor inhibitor treatment.

Methods

We searched peer-reviewed literature on the PubMed database using key words “androgen-deprivation therapy,” “androgen receptor inhibitors,” “bone,” “bone complications,” and “nonmetastatic prostate cancer” from 2000 to present.

Results

We discuss how androgen inhibition affects bone health in patients with nonmetastatic castrate-resistant prostate cancer. We present data from phase 3 trials on the three approved androgen receptor inhibitors with regard to effects on bone. Finally, we present management strategies for maintenance of bone health.

Conclusions

In patients with nonmetastatic castrate-resistant prostate cancer, aging, and antiandrogen therapy contribute to bone fragility. Newer androgen receptor inhibitors were associated with falls or fractures in a small subset of patients. Management guidelines include regular assessment of bone density, nutritional guidance, and use of antiresorptive bone health agents when warranted.

onclive.com

Giri and Gomella on Fostering a New Framework for Genetic Testing Guidelines in Prostate Cancer

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In our exclusive interview, Dr. Giri and Dr. Gomella discuss the rationale to create the first multidisciplinary, consensus-driven framework for prostate cancer genetic testing, the importance of having a multidisciplinary team weigh in on the recommendations, and key aspects of the guidelines that could have clinical implications for men in this space.

https://www.onclive.com/view/giri-and-gomella-on-fostering-a-new-framework-for-genetic-testing-guidelines-in-prostate-cancer

Welcome to a very special edition of *OncLive*® On Air! I'm your host today, Jessica Hergert.

OncLive® On Air is a podcast from *OncLive*, which provides oncology professionals with the resources and information they need to provide the best patient care. In both digital and print formats, *OncLive* covers every angle of oncology practice, from new technology to treatment advances to important regulatory decisions.

Today, we had the pleasure of speaking with Veda N. Giri, MD, and Leonard G. Gomella, MD, both of Thomas Jefferson University Hospital, to discuss the **first multidisciplinary, consensus-driven framework for prostate cancer genetic testing**.

Borne out of the 2019 Philadelphia Prostate Cancer Consensus Conference, the comprehensive guidelines shed light on the evaluation, management, and implementation of genetic testing for men with prostate cancer or men with an increased risk of developing prostate cancer.

Notably, the guidelines strongly recommend both germline and somatic genetic testing for all men with metastatic prostate cancer. Additionally, the framework recommends that all men with a family history that could indicate an increased risk of hereditary prostate cancer or other cancers, including breast, ovarian, pancreatic, and colon cancer, should receive reflex testing to determine whether active surveillance or screening is recommended.

Listen on to hear Dr. Giri, lead study author of the guidelines, and director of the Cancer Risk Assessment and Clinical Cancer Genetics Program and the Men's Genetic Risk Clinic at the Sidney Kimmel Cancer Center, and Dr. Gomella, chair of the Department of Urology at Sidney Kimmel Cancer Center, as well as co-chair of the 2019 Prostate Cancer Consensus Conference, discuss the rationale to create these guidelines, the importance of having a multidisciplinary team weigh in on the recommendations, and key aspects of the framework that could have clinical implications for men in this space.

health.harvard.edu

New online model identifies which men can have fewer biopsies on active surveillance - Harvard Health Blog

Charlie Schmidt

During the last decade, more men with favorable-risk prostate cancer that is unlikely to cause symptoms and spread have opted for a monitoring approach called active surveillance (AS) instead of immediate treatment. AS entails routine PSA checks and prostate tumor biopsies, and the cancer is treated only if it progresses. The approach has some drawbacks, especially because repeat biopsies — which are standard for monitoring the cancer's behavior — are expensive and uncomfortable, and carry a small risk of infection.

Now researchers are concluding that some men on AS don't need to be re-biopsied as frequently as others. Dr. Matthew Cooperberg, a urologist at the University of California San Francisco, says a one-size-fits-all approach to scheduling biopsies "makes little biological sense," given that prostate cancer varies so widely in terms of its behavior after diagnosis.

Current protocols call for biopsies every one to three years. But Cooperberg and his colleagues wanted to know if they could identify men who could proceed safely with an even less intensive schedule.

To find out, they reviewed data from two large AS cohorts: one is run by the Canary Prostate Active Surveillance Study, which is ongoing at nine centers in North America; the other is based at UCSF. The team focused on nearly 1,400 men who were diag-

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nosed between 2003 and 2017 and then followed for an average of four years. They identified several factors that predict if a man's cancer might turn more aggressive: the number of positive biopsy cores at diagnosis; PSA levels at diagnosis, and the rate at which they change over time; and a history of any subsequent negative biopsies after a man has already been diagnosed with prostate cancer.

Plug and play

The researchers incorporated these and other factors into an online model that shows where men fall on the risk spectrum. Findings from the research suggest that "large subpopulations of men might be able to defer additional biopsies and even many interval PSA tests," the authors wrote. But importantly, the model doesn't advise men as to whether they should get a biopsy or not. "It's not a yes or no test," Cooperberg says. Instead, the calculator "uses all the available information at hand to get a more precise assessment of risk for shared decision-making between a man and his doctor."

Cooperberg said doctors may eventually use other types of predictive information, such as magnetic resonance imaging or tests for genetic biomarkers, to identify men who might avoid biopsies altogether. These newer tools are currently under investigation and haven't been endorsed in clinical AS guidelines. "We'd like to do AS without any biopsies at all and tell a significant proportion of men that they're never going to develop aggressive cancer," Cooperberg said. "But we're not there yet."

"This study underscores the important research that is ongoing to help minimize invasive procedures for clinically localized prostate cancer in men who opt for active surveillance," said Dr. Marc Garnick, the Gorman Brothers Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center, and editor in chief of HarvardProstateKnowledge.org. Garnick added that in his practice, patients who have completely stable repeat biopsies for several years, as well as stable prostate MRI studies, are followed with a combination of "PSA values, physical exam, presence or absence of urinary symptoms, and periodic MRI studies." Under these conditions, additional biopsies are considered if findings from these other tests suggest an increase in cancer activity. The new predictive model, Garnick added, "should provide data that can help inform this decision, with the hope and anticipation that longer-term research will continue to justify less frequent biopsies."

On the Lighter Side