Informed Prostate Cancer Support Group Inc.
"A 501 C 3 CORPORATION ID # 54-2141691"

September 2019 NEWSLETTER

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We Meet The Third Saturday of Each Month
(except December)

Sunday, September 15,

Volume 12 Issue 9

Next Meeting: , September 21, 2019 –Member Roundtable

A panel of members will discuss their experiences, what treatments they choose, how they are doing today, and pass along their lessons learned. Then the group will break-out into sessions by treatment type (Active Surveillance, Surgery, ADT, Radiation, Chemo) for networking. This is when you can get all your questions answered by other members who are currently going through treatment, or have had treatment. All areas related to prostate cancer will also be discussed.

- **For further Reading:** https://spendergast.blogspot.com/2019/03/prostate-cancer-news-of-interest-for.html
- **For Comments, Ideas and Questions,** email to Newsletter@ipcsg.org

August 2019 Informed Prostate Cancer Support Group Meeting:
How to Manage Our Case – an interactive discussion with George Johnson and Gene Van Vleet

Summary by Bill Lewis

1. **Why and How We Should Manage Our Own Case:** You are the most important person on your prostate cancer (PCa) health-care team. You are the expert on you! Your doctor has thousands of patients and only allots a few minutes for your visits. There are choices to be made. Take time to think about your personal goals and the therapy for your life style. Get a second (third?) opinion on diagnostics and treatment decisions. Get copies of all medical reports and tests, keep a file and track the changes over time. Take the file to your appointments for your questions, and write answers.

Here are elements of PCa case management knowledge that are covered in IPCSG meetings, most of which you will not learn about from your doctor: PSA TESTING, BIOPSIES, GLEASON & STAGE, TREATMENT OPTIONS, PARTIN TABLE, DOUBLING TIME, ADT PRETREATMENT, ACTIVE SURVEILANCE, PSA SHIFT POST-TREATMENT, ADT SIDE EFFECTS, DIET – DAIRY PRODUCTS/PROTEIN, PSA STANDING ORDER, TARGETED BIOPSY, DIHYDROTESTOSTERONE, T & DHT TESTING, PSA TESTING FREQUENCY, CASODEX/AVODART, FEMARA, ADT INTERMITTENT, PSA 2X AVODART, PRIMARY PCa TUMOR, NEW TREATMENT OPTIONS, PARTICIPATION IN CLINICAL TRIALS. If you are not familiar with all of these, keep coming to the

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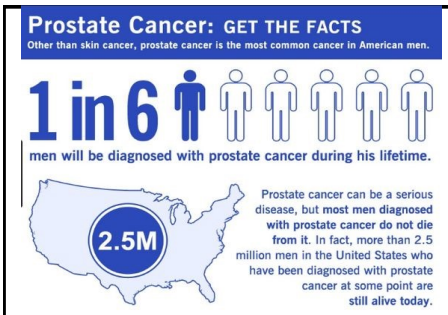

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a 501c3 non-profit organization - all positions are performed gratis

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Stephen Pendergast ..... Editor

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.

Be your own health manager!!

Meeting Video DVD's

DVD's of our meetings are 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.

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

From the Editor
In the Newsletter this Month

As usual, Bill Lewis provides a fine summary of George and Gene's talk last month on managing your case. Of course, purchase of a DVD will provide video of the meeting and copies of slides.

In articles of interest, an article from Prostate Cancer Infolink addresses the trends in use of Complementary and alternative medicines, e.g., vitamin D and acupuncture. In an article from Medscape covers use of CTC blood test and gene expression analysis in the UK to supplement PSA tracking for staging Cancer and reducing unnecessary biopsies which should be of interest for AS. Then an article from Cancer ABCs covers the effectiveness of supplementary resection or spot radiation for men with metastases to the lymphatic nodes. Lastly, an article from Onclive discuses the many new techniques for attacking stage 4 advanced castrate resistant PCa.

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; VP Gene Van Vleet @ 619-890-8447; or **Meeting facilitator** George Johnson @ 858-456-2492.

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IPCSG meetings and use all the IPCSG resources!

2. **What's Different About Prostate Cancer:** It's slow growing for 85% of men. Through PSA testing, it can be detected early, and can be confirmed by biopsy. The complexity of the pelvic area is an important consideration for treatment options. Technology developments are constantly leading to new kinds of advanced treatments. As treatment options expand, second opinions are vital. PCa is the only cancer where the patient almost always sees a surgeon (a urologist) first instead of an oncologist.

3. **Case Tracking, Things You Should Know and Measure:** a) Understand your Gleason score. This is a measure of risk, the aggressiveness and likelihood of recurrence. The two grade numbers that add up to your Gleason Score are as important as the total. A 3 + 4 = 7 Gleason is different than a 4 + 3 = 7 Gleason. The first is low intermediate risk, the second is high intermediate risk. The first number represents the grade of the most common type of cancer found in the biopsy sample. The second number represents the grade of the next most common. A total Gleason Score from 6 to 10 indicates the aggressiveness of the cancer. Get a second opinion on the biopsy samples, preferably from Johns Hopkins. See contact info below.

The genetic features (the molecular nature) of Gleason 3 + 3 = 6 cells are completely different from higher grades. The DNA is profoundly different from cells of the Gleason 4 pattern, and there is a big difference in risk. A Gleason 3 cell does not grow into a Gleason 4 cell. However, even if a patient has biopsy results giving a 3 + 3 Gleason score, there is a small chance that some Gleason 4 cells are present but undetected.

b) Know the stage. This is a measure of location & spreading. It is measured by an analysis of the cancer location within & outside the prostate from the biopsy and DRE (digital rectal exam). Definitions of the various stages are readily available on the internet.

c) Follow the PSA, both the value and its doubling time. The "doubling time" is the measure of the aggressiveness of the cancer – the months or years it takes for the PSA to double. The frequency of PSA testing needs to be less than your doubling time to best manage your case, and the rate of rise indicates the urgency for treatment, or for a change in treatment.

d) Use the PARTIN TABLES. These are biopsy statistics from Johns Hopkins on the probabilities of PCa (still) being contained in the prostate "capsule," and provide an important element in considering treatment options. Print and discuss your Partin results with your doctor! Google "partin tables" and fill in your numbers in a table that will come up when you select the first search result, which is the "Johns Hopkins James Brady Urological Institute."

This will give you the probabilities that your cancer is confined to the capsule or has likely invaded other locations. For example, a man with PSA = 6 to 10, Gleason 3 + 4 = 7, and stage T2A has a 58% chance that his cancer is "organ confined," but a 36% chance that there is "extra prostatic extension" of the disease, with only a 4% chance that the seminal vesicles have been invaded, and a 2% chance that lymph nodes are diseased. In contrast, with PSA greater than 10, Gleason 4 + 3 = 7, and stage T2C, there is only a 12% chance that the cancer is organ confined, a 33% chance that there is extra prostatic extension, a 22% chance that the seminal vesicles have been invaded, and a 32% chance that lymph nodes are diseased. These different probability profiles imply a need for very different treatments, and a printout of your profile should be discussed with your doctor.

4. Factors in Standard (Random) or Targeted Biopsies: Biopsies are the primary means of accurately detecting/identifying cancer cells. Prostate cancer is the only cancer where most doctors do not target the biopsy needles at suspected tumor sites. These doctors use a standard or "systematic" 12-needle grid pattern, which may miss a tumor. They use ultrasound to outline the prostate, not to locate tumors. It's a random procedure; hit & miss (a lot). In contrast, the best doctors use advanced MRI fusion (or in-bore) biopsy to locate and aim at suspected tumors.

After a biopsy, the tissue "cores" are examined and Gleason grades are assigned and combined into a score from 6 to 10, as discussed in section 3 above. Whereas a simplified "cartoon" sketch of differences between grades is often seen in the media, the reality is that differences are very subtle and subjective, so it is very important to get a second opinion.

5. **Do You (And the Doctors) Know Where Your Cancer Is?** Common tests after a biopsy are Bone scans, CT/CAT scans and MRI's. These are particularly important for the 15% of patients who have a rising PSA, a short doubling time (months, not years), a Gleason Score >6, or a recurrence after treatment. Of these tests, only the biopsy can specifically confirm the presence of PCa tumors, but the others can still help with the dilemma of identifying capsule penetration and suggest where it has spread, so that decisions for treat-

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ment will be appropriate. New tests, including Carbon C-11, Axumin PET/CT and PSMA PET/CT are specific for prostate cancer, but insurance coverage is currently only available for Axumin scans.

6. **Questions to Ask Your Doctor:** Initial Visit: If your father had my PCa, what would you recommend? How many patients have you treated? What is your recommendation for me? Alternative Plans (Options)? What are the possible side effects? When will they occur, and duration? Can the side effects be treated? What about _____ (something from the internet, IPCSG, etc.)?

Follow-up Visits: Overall, how am I doing? What's my level of risk / cancer aggressiveness? What do the test results mean? What's the next step? When should I get my next PSA Test? What is my doubling time?

7. Doctor Selection Process for & When to Ask for a 2nd Opinion: a) Get a second opinion after the biopsy to validate a Gleason Score of 6 or above. Call Dr. Epstein at Johns Hopkins, 410-614-6330. b) Certainly before an invasive treatment selection, to seek options and discuss Quality of Life effects. Ask your doctor for his/her recommendation, but avoid doctors in same HMO & hospital -- seek out independent doctors.

8. Treatment Selection & Quality of Life Considerations: Do not rush your decision – your treatment decision is yours to make. Do not take the quick step toward surgery because of a macho approach to "cut the damn thing out" without learning about the side effects of this decision vs. your alternatives. Learn more about quality of life factors. Many men who have rushed for remedies have had second thoughts after one or two years. Your best initial action could be Active Surveillance rather than starting an invasive procedure. Ask your doctor if this could be more appropriate to start your program. If he suggests a more invasive treatment, ask about the side effects and other options. Get details. And, as noted above, get second opinions.

Possible side effects of treatments: Impotence, Weight Gain, Bone Loss, Incontinence, Urinary Frequency, Libido Loss, Diarrhea, Penile Shortening, Muscle Loss, Hot Flashes, Heart Effects, Depression, Breast Enlargement, Fatigue, Erectile Dysfunction. Emphasize to your doctor how much a side effect is bothering you, or he is likely to ignore your concern. Here's a summary from the Prostate Cancer Research Institute showing their estimates of likelihood of many side effects:

9. Developing a Positive Approach to Your Recovery: Join a support group and talk with other patients about their treatments, their decision process and their quality of life issues. Check the library for books and discs. Remain positive – 95% of those who have prostate cancer survive 10 years if treated. The most powerful tool to guide you in your journey through cancer is knowledge. Learning about your condition can give you confidence, comfort and put you in control. Remember the three "E's": Endurance (Be active, diet, exercise, talk to and help others), Encouragement (for self and others), and Enthusiasm (go have some fun, here and elsewhere).

Questions:

What places in San Diego have the most experienced doctors for PCa treatments? UCSD Moores Cancer Center does the most surgeries. More and more people are choosing radiation because it has fewer side effects. Dr. Kane, Dr. McIntire and Dr. Carol Salem are considered the best local surgeons. Propublica has data through 2013 on doctors performing prostatectomies (see https://projects.propublica.org/surgeons/), and it shows that Dr. Salem has the lowest rate of complications.

What's the significance of the PSA – is it the best measure of how fast the PCa is growing? The PSA test is not diagnostic for cancer. PSA is like the "check engine" light on your car. It means that you have an irritation, an inflammation, or infection. Only a biopsy can confirm whether it is cancer. If it is, then the PSA doubling time (years, months or weeks) becomes very important as a measure of PCa aggressiveness. But George said that his undifferentiated PCa cells don't generate PSA, so PCa can be present even if the PSA is low – though this is a rare situation. See also a member comment below, about the PAP test.

Side Effect	SURGERY	RADIATION	ADT	AS
ED (erectile dysfunction)	+++	++	++++	-
Libido Loss	++	+	++++	-
Penile Shortening	++	+	++++	-
Incontinence	++	++	-	-
Urinary Frequency	+	++	-	-
Bowel Problems	-	++	-	-
Bone Loss	-	-	+++	-
Hot Flashes		-	++++	-
Muscle Loss	-	-	+++	-
Fatigue	-	+	++	-
Anxiety	-	-	+	+++

It was noted by Stephen Pendergast that although a Gleason 3 cell won't transform into a Gleason 4 cell,

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your biopsy results could change, as his did. A biopsy samples only a tiny percentage of the prostate, and a later biopsy may find some cells – a tumor – of higher grade, more aggressive cells. He also asserted that patients taking medicine (such as Avodart) for BPH should recognize that the PSA would be twice as high in the absence of the medication. George responded that it's a controversy as to whether this is true.

Another member noted that PSA density is another factor to consider. This number is the PSA divided by the prostate volume, and recognizes that a large prostate naturally produces more PSA than a small one.

The best approach for a biopsy, according to Gene Van Vleet, is to target the needles using Fusion MRI, to aim right at suspicious spots, rather than just having a "systematic" (random) 12-core biopsy. This is also the best method to keep tracking the PCa – keep watching with mpMRI, and do a biopsy if there are changes. George agreed, and said that an initial mpMRI can help make sure that the biopsy targets the "mother tumor," which often is missed in random biopsies.

How much information can you get from the MRI report (without doing a biopsy)? If you get an mp-MRI (not just a standard MRI), it will tell you where the tumor is [with high likelihood, if it is clinically significant], and how big it is. If treatment doesn't seem needed, you might compare that "baseline" scan with another scan in six months, and see if anything has changed.

A member's comment: 10 yrs ago, a biopsy showed "indeterminate cells." Two years ago, he had blood in the semen and an increasing PSA, and his urologist talked him out of getting a biopsy. Now he has Gleason = 9 cancer in the area previously identified, and his doctor's comment was, "Well, you didn't get that overnight." You really need to be aggressive about what you think needs to be done, all along the way.

Another comment, from a wife whose husband has metastases. She highly recommends getting a second opinion and getting to an oncologist at UCSD. It's not that expensive and was necessary for her husband, to get better care than he was getting from his HMO. Gene noted that he can provide the name of a person who is very helpful in getting the best insurance coverage.

Who in San Diego do you recommend for MRI-guided biopsies? Imaging Healthcare Specialists, available on referral from an oncologist or urologist.

A comment: A member had a PSA of only about 4, but metastasized, aggressive cancer. His oncologist (Dr. Lam) uses a second test, called the PAP (prostatic acid phosphatase) test, which can help to indicate possible extra-prostatic disease.

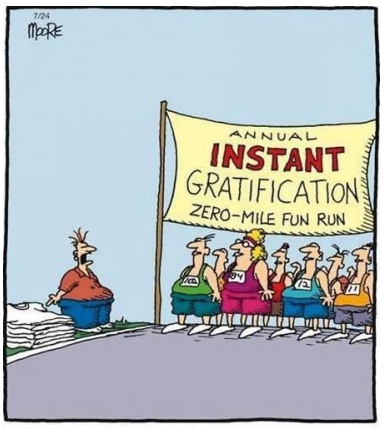
How many in the group had surgery, then recurrence, and how many had radiation, then recurrence? There were some of each, but George and Gene pointed out that our group has a higher percentage of people who have had those recurrences than a "normal" population, since our group has men seeking information and answers to problems. George recommended getting regular PSA tests after treatment, to watch for recurrence.

Has Lutetium-177 helped any members? No, among five who have tried it.

What have people found useful in reducing side effects of ADT? For stress/depression, Effexor or Cymbalta (also helpful for hot flashes – especially for young men) and Wellbutrin. Routine exercise that includes cardio and weight or resistance training.

More details are given in the video of this presentation, including the PowerPoint slides, which will be available for purchase via the website shortly before the next meeting, or at the September meeting on the 21st.

On the Lighter Side



"Runners to your mark. Get set. Go! ... OK, come get your T-shirts."

"I know the kids don't like you and pick on you, but you have to go to school...you're the teacher."

Articles of Interest

Complementary and alternative medicines in management of prostate cancer

prostatecancerinfolink.net Posted on September 13, 2019 by Sitemaster

https://prostatecancerinfolink.net/2019/09/13/complementary-and-alternative-medicines-in-management-of-prostate-cancer/

A newly published paper in the Journal of Urology has reported on the use of complementary and alternative medicines (CAMs) among a cohort of nearly 8,000 American patients with a diagnosis of prostate cancer between 1996 and 2016.

This paper by Zuniga et al. (https://www.auajournals.org/doi/pdf/10.1097/JU.0000000000000336) analyzed data from a total of 7,989 men in the CaPSURE database over a 20-year time frame and included information on the use of nearly 70 different forms of complementary and alternative medicines by prostate cancer patients — i.e., things like vitamins, omega-3 fatty acid, green tea, etc.

The authors found that there had been significant changes in the popularity of specific forms of such medicines over time. Most notably:

Among men diagnosed between 2011 and 2016, compared to men diagnosed between 1996 and 2000, there was

- A relative increase of 128 percent in use of all CAMs (from 24 to 54 percent)
- A relative increase of 108 percent in use of **vitamin D** supplements
- A relative decrease of 48 percent in use of vitamin E supplements
- A very large relative increase of 259 percent in the use of **acupuncture**
- A significant decrease of 65 percent in the use of selenium supplements

However, …

What this paper does not comment on is the effectiveness or the safety of use of such products, and so one has to be very careful to differentiate between whether behavior of patients has changed over time (which is what this paper shows) and actual usefulness of the CAMs discussed.

We can have a pretty clear idea why the use of vitamin E and selenium supplements dropped over these two time periods. This is — with near certainty — a consequence of the results from the 35,000-man, randomized, double-blind SELECT trial. That trial showed that taking selenium supplements led to a small but statistically insignificant increase in the risk that a man would be diagnosed with prostate cancer and that vitamin E supplements actually increased risk for diagnosis with prostate cancer significantly.

The value of most dietary modifications and CAMs in the management of prostate cancer over time remains unproven. On the other hand, there are clear benefits to overall survival from appropriate weight loss and exercise, and so dietary modifications that assist in appropriate weight loss are clearly a good idea. In saying this, we wish to emphasize that we are not denying the fact that many prostate cancer patients feel and believe that the use of CAMs and dietary modifications improve their quality of life and perhaps their overall survival. So long as there is no known harm associated with the use of such CAMs, we believe it is appropriate for patients to discuss such options with their doctors and come to a shared decision about what might work well for them.

Filed under: Diagnosis, Living with Prostate Cancer, Management, Risk, Treatment | Tagged: alternative, CAM, complementary, medicine

Adding a CTC Test May Improve Prostate Cancer Diagnosis

Helen Leask

https://www.medscape.com/viewarticle/918362?src=rss

A novel blood test for prostate cancer has the potential to significantly improve patient stratification by prostate-specific antigen (PSA) and/or multiparametric MRI for biopsy and treatment, say the authors of a new study published online August 7 in the Journal of Urology. (https://www.auajournals.org/doi/10.1097/JU.0000000000000475)

The noninvasive diagnostic tool, which uses circulating tumor cell (CTC) analysis, can also identify clinically significant prostate cancer in pre-biopsy patients with high accuracy.

The benefits of such a tool might allow men to avoid biopsy and its risks of bleeding and infection, say lead author Yong-Jie Lu, MD, PhD, Queen Mary University of London, UK, and colleagues.

In the study, researchers enrolled 155 patients with treatment-naive prostate cancer and 98 pre-biopsy patients for CTC tally. RNA was extracted from the cells of 184 patients for gene expression analysis

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In localized prostate cancer patients, 54% were scored as CTC positive, which was associated with higher Gleason score (P = .0003), risk group (P < .0001), and clinically significant prostate cancer (P < .0001). In the pre-biopsy group, positive CTC score in combination with PSA predicted clinically significant prostate cancer (AUC, 0.869).

The authors also state that a 12-gene panel prognostic for clinically significant prostate cancer was also identified. When that panel was combined with PSA level and CTC score, the AUC for clinically significant prostate cancer prediction was 0.927. Additionally, in cases with multiparametric MRI data, adding these tools to multiparametric MRI significantly increased the prediction accuracy (AUC, 0.936 vs 0.629).

The authors stress that, as this is a single-center study, the results need independent validation before the test becomes available to patients, which could take 3 to 5 years. Any subsequent approval by the US FDA could also take 3 to 5 years, according to the Queen Mary University of London press office.

There's a lot of room for improvement in the diagnosis of prostate cancer, say the authors.

They remind that prostate cancer is currently detected using PSA levels followed by a biopsy of the prostate. PSA can provide early diagnosis but is notoriously inaccurate. Half of men who test PSA positive do not have cancer on biopsy. Also, some prostate cancers are not fatal and can be left untreated, but it is difficult to reliably pinpoint these cancers. This means that many men with a high PSA go on to unnecessarily endure biopsy, surgery, and other treatments, with their attendant risks of bleeding and infection, and in the case of radical prostatectomy, urinary incontinence and erectile dysfunction.

"The issue with prostate cancer is that we want to detect the clinically significant cancer, but more than half of patients with elevated PSA don't have clinically significant cancer," said Lu.

PSA is not ideal because it has high sensitivity — meaning someone with prostate cancer will [*almost,* ed.] always have high PSA — but low specificity — meaning it generates a lot of false positives (patients who have a high PSA but don't have cancer) said Lu.

Salvage Lymph Node Dissection May Delay Prostate Cancer Recurrence — Cancer ABCs

https://www.cancerabcs.org/advanced-prostate-cancer-blog/2019/9/11/salvage-lymph-node-dissection-may-delay-prostate-cancer-recurrence

A preliminary study showed that along with systemic therapies, salvage lymph node dissection (removal) in men with non-metastatic (M0) castration-resistant prostate cancer might delay cancer recurrence.

More research is still needed to confirm this result says Luca Boeri, MD, of Mayo Clinic, Rochester, MN, who presented the results at the 2019 AUA annual meeting in Chicago.

This result is significant because non-metastatic, castration-resistant prostate cancer is a relatively indolent disease, and there is no high-quality evidence to guide clinical decision-making. Currently, the standard of care for men who do not exhibit evidence of bone or visceral metastases are typically managed with observation or ADT.

The retrospective study conducted by Dr. Boeri, working with R. Jeffrey Karnes, MD, and colleagues at Mayo Clinic analyzed men with node-only recurrence who were treated with salvage lymph node dissection or systemic therapies from January 1990 through January 2016. These men underwent a positron emission tomography/computed tomography scan and conventional imaging to detect possible metastases (detected at 11C-choline PET/CT).

Among the men in this cohort, 23 (51%) underwent salvage lymph node dissection for lymph node-only recurrence of castration-resistant prostate cancer, and 22 (48.9%) received systemic therapies (ADT or chemotherapy) for lymph node-only recurrence of castration-resistant prostate cancer.

ADT patients were treated with a different medication—either alone or in combination with the previous ADT drug used—based on the physician's discretion. All salvage lymph node dissection procedures were performed by a single surgeon between Nov. 1, 2009, and Dec. 31, 2016.

Biochemical recurrence was defined as a PSA greater than 0.2 ng/mL with an increased trend, while radiologic recurrence was described as a positive imaging study or biopsy-proven metastasis after salvage lymph node dissection or systemic therapies.

Median follow-up for the entire cohort was 49.3 months

The results point to the potential for salvage lymph node dissection to be used as a treatment option in men with node-only recurrence of castration-resistant prostate cancer:

• Mean PSA reduction was significantly higher after

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salvage lymph node dissection than after ADT (62.8% vs. 17.4%).

• Time to PSA nadir was significantly lower in the salvage lymph node dissection group than the ADT group (1.6 months vs. 7.3 months).

• The 5-year cancer-specific mortality rates were 72.7% and 72.3% for salvage lymph node dissection and ADT patients, respectively.

• There was a trend toward a longer time to biochemical recurrence (13.3 months vs. six months) and radiologic recurrence (21.1 months vs. 14.2 months) in salvage lymph node dissection patients than ADT patients.

• The median time to standard systemic therapy was longer in the salvage lymph node dissection group than that ADT group (66.1 months vs. 43.3 months)

However, one limitation of the study—in addition to the small sample size—is that the results are based on traditional imaging techniques.

Search for New Prostate Cancer Targets Yields a Profusion of Options

Figure. Multiple Mechanisms Implicated in Prostate Cancer

https://www.onclive.com/publications/Oncology-live/2019/vol-20-no-17/search-for-new-prostate-cancer-targets-yields-a-profusion-of-options

Despite the introduction of novel therapies over the past decade, advanced prostate cancer remains an incurable disease in need of new strategies to overcome drug resistance. Investigators are exploring many approaches, including more potent antiandrogen agents, immune checkpoint immunotherapies, and molecularly targeted drugs Androgen deprivation therapy (ADT) remains the backbone of treatment for advanced tumors, but patients will invariably relapse and transition to a particularly challenging castration-resistant state. Consequently, prostate cancer is the second-leading cause of cancer-related mortality among men in the United States.

An improved understanding of the mechanisms underlying prostate cancer has led to the development of a new generation of androgen receptor (AR) antagonists being introduced earlier in the treatment timeline. Over the past 18 months, the FDA has approved apalutamide (Erleada) and darolutamide (Nubeqa) for patients with nonmetastatic castration-resistant prostate cancer (CRPC).

Meanwhile, immunotherapies aimed at the PD-1/PD-L1 pathway and small molecules targeting PARP are among many targets in development, according to information on the ClinicalTrials.gov website (Table).

Although efforts to target the PI3K pathway and to cash in on the success of immunotherapy in other tumor types have resulted in some disappointment, ongoing research into combination strategies and potential biomarkers of response is generating promising signals.

Androgens in the Driver's Seat

Prostate cancer has long been recognized as a hormonally driven disease.

Nobel Prizewinning research conducted in the 1940s heralded the introduction of ADT,3 the goal of which is to reduce circulating levels of androgens, consisting predominantly of testosterone and its derivative, 5-dihydrotestosterone, to curb prostate cancer growth.7

Androgens are essential for the development and normal function of the prostate. They bind to the AR in the cytoplasm of target cells, releasing the receptor from an inactive protein complex and allowing it to move into the nucleus, where it orchestrates cellular effects by binding to androgen-responsive elements, inducing transcription of target genes.8,9 Many of these target genes are involved in the growth and survival of prostate cancer cells, and aberrant activation of AR signaling has been strongly implicated in the development of prostate cancer.

ADT is achieved either surgically, through removal of the testes, or chemically, through the use of drugs that block the activity of luteinizing hormone-releasing hormone (LHRH), which stimulates production of testosterone by the testes. Because other parts of the body can produce testosterone, neither surgical nor chemical castration completely eliminates androgens.3,7

This obstacle prompted the development of antiandrogens, drugs designed to block the body's ability to use androgens by inhibiting the activity of the AR. The first nonsteroidal antiandrogens—bicalutamide, nilutamide, and flutamide—were effective at achieving maximal AR blockade but did not prevent development of CRPC.

Intensive research efforts have uncovered at least 3 major mechanisms of castration resistance: bypass signaling, in which cells develop mechanisms to evade AR blockade, through, for example, upregulation of the closely related glucocorticoid receptor; changing phenotype, which involves dedifferentiation into a neuroendo-

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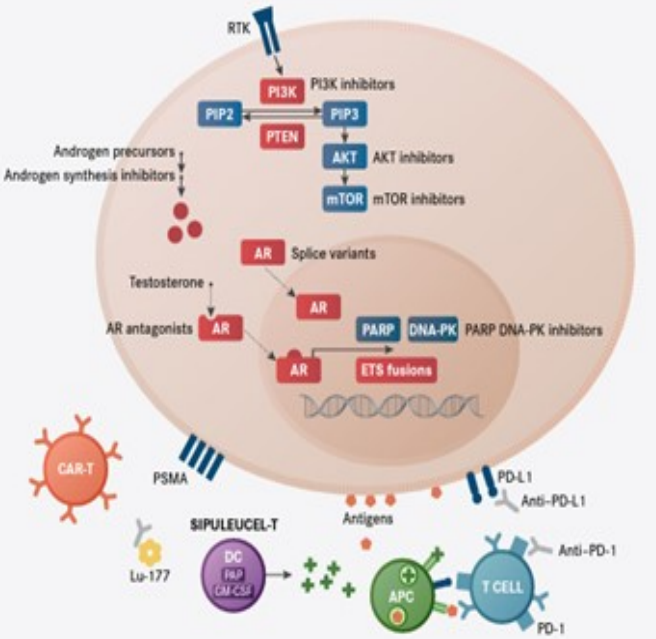
crine form of prostate cancer; and reactivation of AR signaling, which can be achieved in many ways, including via AR gene amplification, AR protein overexpression, mutations in the AR ligand-binding domain, and AR splice variants.

By leveraging a greater understanding of CRPC biology, investigators developed enzalutamide (Xtandi), a second-generation, more potent AR antagonist. The FDA first approved the drug in 2012 for patients with metastatic CRPC (mCRPC) previously treated with docetaxel. The agency recently expanded the approval to include all patients with CRPC, even nonmetastatic cases, based on the results of the PROSPER trial, which demonstrated a statistically significant improvement in metastasis-free survival (MFS) compared with placebo (36.6 vs 14.7 months, respectively; HR, 0.29; P <.0001).

FIGURE. MULTIPLE MECHANISMS IMPLICATED IN PROSTATE CANCER[1,2]



A growing understanding of the biology of prostate cancer has led to the expansion of strategies for attacking mechanisms that promote initial disease and resistance to antiandrogen therapies.

APC, antigen-presenting cell; AR, androgen receptor; CAR, chimeric antigen receptor; DC, dendritic cell; DNA-PK, DNA protein kinase; GM-CSF, granulocyte macrophage colony-stimulating factor; PIP, prostate inhibin peptide; PSMA, prostate-specific membrane antigen; RTK, receptor tyrosine kinase.

Recreated from Shevrin, DH. *Asian J Androl*. 2016;18(4):586-591. doi: 10.4103/1008-682X.177121 and Considine B, Petrylak DP. *Oncology (Williston Park)*. 2019;33(3):113-118.

TABLE. NOVEL AND ESTABLISHED AGENTS UNDER STUDY IN PROSTATE CANCER

Drug (Developer or Sponsor)	Mechanism of Action	Phase(s) of Development
PI3K pathway inhibitors		
GSK2636771 (GlaxoSmithKline)	Selective inhibitor of PI3Kβ	I
AZD8186 (AstraZeneca)	Selective inhibitor of PI3Kβ	I
Ipatasertib (Roche)	AKT inhibitor	I; I/II; III
Capivasertib (AZD5363) (AstraZeneca)	AKT inhibitor	I
Everolimus (Afinitor) (Novartis)	mTOR inhibitor	III
Sirolimus (Rapamune) (Pfizer)	mTOR inhibitor	I/II
MK-2206 (National Cancer Institute)	AKT inhibitor	I-II
CC-115 (Memorial Sloan Kettering Cancer Center)	Dual mTOR/ DNA-PK inhibitor	I
DNA repair/cell cycle inhibitors		
Olaparib (Lynparza) (AstraZeneca)	PARP inhibitor	II-III
Rucaparib (Rubraca) (Clovis Oncology)	PARP inhibitor	II-III
Niraparib (Zejula) (GlaxoSmithKline/Tesaro)	PARP inhibitor	II-III
Talazoparib (Talzenna) (Pfizer)	PARP inhibitor	I/II; II-III
Palbociclib (Ibrance) (Pfizer)	CDK4/6 inhibitor	II
Abemaciclib (Verzenio) (Eli Lilly)	CDK4/6 inhibitor	II
Ribociclib (Kisqali) (Novartis)	CDK4/6 inhibitor	I/II-II
Onvansertib (Trovagene)	PLK1 inhibitor	II
Anti-androgens		
Enzalutamide; Xtandi (Astellas/Pfizer)	AR antagonist	I; I/II; II-III
Abiraterone (Zytiga) (Janssen)	Androgen biosynthesis inhibitor	II
Apalutamide (Erleada) (Janssen)	AR antagonist	I-III
Darolutamide (ODN-201) (Orion/Bayer Healthcare)	AR antagonist	II-III
TAS3681 (Taiho Oncology)	AR antagonist	I
Proxalutamide (GT0918) (Suzhou Kintor Pharmaceutical)	AR antagonist	II
HC-1119 (Hinova Pharmaceutical)	Deuterated form of enzalutamide	III
ARV-110 (Arvinas)	Targeted degrader of AR	I
IONIS-AR-2.5$_{Rx}$ (Ionis Pharmaceuticals)	Antisense oligonucleotide targeting AR mRNA	I/II
Immunotherapy		
Nivolumab (Opdivo) (Bristol-Myers Squibb)	PD-1 inhibitor	I/II-II
Pembrolizumab (Keytruda) (Merck)	PD-L1 inhibitor	II-III
Durvalumab (Imfinzi) (AstraZeneca)	PD-L1 inhibitor	II
Cetrelimab (JNJ-63723283) (Janssen)	PD-1 inhibitor	I
pTGV-HP (Madison Vaccines)	DNA vaccine targeting PAP	I/II; II
BMS-986253 (Bristol-Myers Squibb)	IL-8 mAb	I/II
PROSTVAC (National Cancer Institute)	PSA-based vaccine	I/II
AZD5069 (AstraZeneca)	CXCR2 antagonist	I/II
Galunisertib (LY2157299) (Eli Lilly)	TGFβR inhibitor	II
PSMA-targeted therapy		
177Lu-PSMA-617 (Endocyte)	PSMA-targeted radioligand	I; I/II; II-III
131I-MIP-1095 (Progenics Pharmaceuticals)	PSMA-targeted radioligand	II
177Lu-J591 (Weill Cornell)	PSMA-targeted radioligand	I/II; II
225Ac-J591 (Weill Cornell)	PSMA-targeted radioligand	I
CART-PSMA-TG-FβRDN (University of Pennsylvania)	PSMA-targeted CAR T cells	I
Other		
CORT125281 (Corcept Therapeutics)	Glucocorticoid receptor antagonist	I/II
ORIC-101 (ORIC Pharmaceuticals)	Glucocorticoid receptor antagonist	I
Metformin (Various)	Antihyperglycemic agent	II
ZEN003694 (Zenith Epigenetics)	BET inhibitor	I/II
Erdafitinib (Balversa) (Janssen)	FGFR inhibitor	II
CPI-1205 (Constellation Pharmaceuticals)	EZH2 inhibitor	I/II
CCS1477 (CellCentric)	Acetylation inhibitor	I/II
Sacituzumab govitecan (IMMU-132) (Immunomedics)	Trop2-targeted ADC	II
AZD4635 (AstraZeneca)	Adenosine A2A receptor inhibitor	I

AR, androgen receptor; BET, bromodomain and extraterminal domain containing proteins; CAR, chimeric antigen receptor; CXCR2, C-X-C chemokine receptor 2; DNA-PK, DNA-dependent protein kinase; EZH2, histone-lysine N-methyltransferase; FGFR, fibroblast growth factor receptor; PAP, prostatic acid phosphatase; PLK1, polo-like kinase 1; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen; TGFβR, transforming growth factor beta receptor; Trop2, trophoblast cell surface antigen 2.

NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Lyle LaRosh, Gene Van Vleet and George Johnson 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

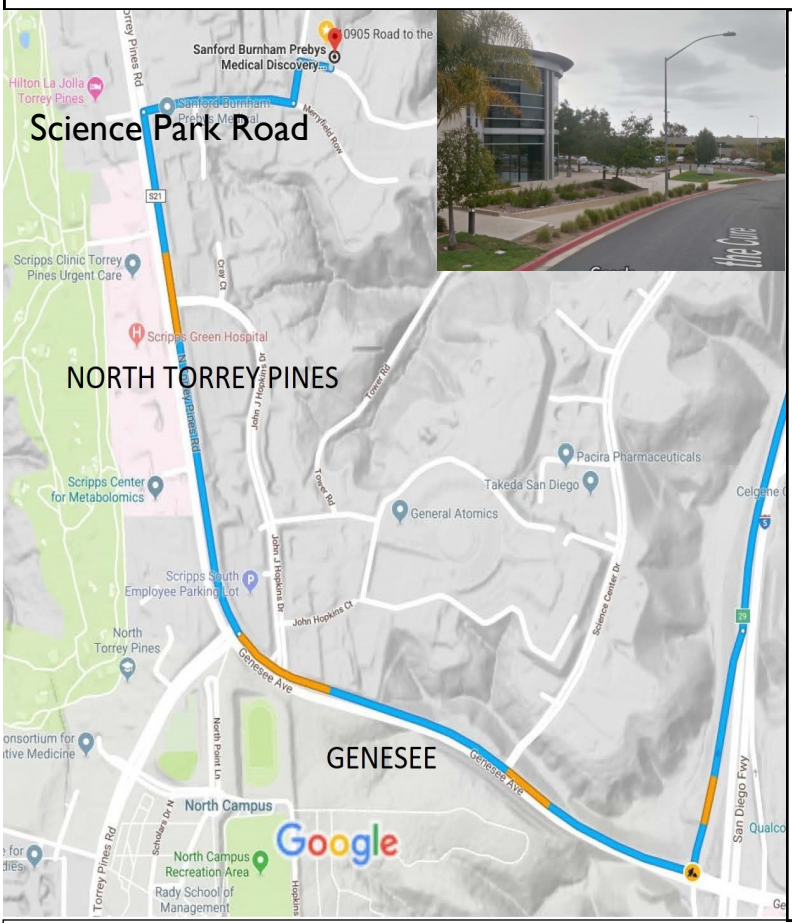
Our brochure provides the group philosophy and explains our goals. Copies may be obtained at our meetings. Please pass them along to friends and contacts.

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!

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 4201042, San Diego CA 92142



Directions to Sanford-Burnham-Prebys Auditorium
10905 Road to the Cure
San Diego, CA 92121

- Take I-5 (north or south) to the Genesee exit (west).
- Follow Genesee up the hill, staying right.
- Genesee rounds right onto North Torrey Pines Road.
- **Do not turn into the Sanford-Burnham-Prebys Medical Discovery Institute or Fishman Auditorium**
- Turn right on Science Park Road. Watch for our sign here.
- Turn Left on Torreyana Road. Watch for our sign here.
- Turn Right on Road to the Cure (formerly Altman Row). Watch for our sign here.