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

Wednesday, March 16,

MARCH 2022 NEWSLETTER

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STREAMING ONLINE LIVE

Volume 15 Issue 03

- **Next Meeting Saturday, March 19, 2022 IPCSG - Live-Stream Event, 10:00am PT**.
- Three members of the IPCSG group will share stories about their journey with Prostate Cancer. This is a great time to ask your questions from men who have gone through different treatments, their successes', difficulties and lessons learned. A brief Q &A session will be after each speaker, then a combined session after all 3 have spoken. This is your chance to get all your questions answered by men who have "been there, done that"..
- 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
- **If you would like some copies of our new brochure by mail for distribution to your friends or physicians, please send email to Newsletter@ipcsg.org or call Gene at 619-890-8447**

February 2022 Informed Prostate Cancer Support Group Meeting
Summary by Bill Lewis

Management of Rising PSA after Primary Treatment

Speaker: Dr. Charles "Chuck" Metzger, MD, MBA; a retired urologist in Glendora CA (near the City of Hope hospital) who is up-to-date about Prostate Cancer.

Men with a rising PSA after primary treatment represent the largest new group of patients. It's almost a secret that the prostate cancer (PCa) recurrence rate is as high as 30-40%, especially after surgery. Included are men who are doing Active Surveillance, following a variety of protocols.

Men with rising PSA may have **oligometastatic** disease – includes de novo (newly diagnosed) and metachronous (men after primary treatment) having less than 5 lesions, or **polymetastatic** disease – more than 5 sites of spread. A traditional bone scan is not very accurate as to number, size and location of metastases. Similarly, a CT scan of the abdomen and pelvis is not usually helpful in early disease. But now, F18 PET and/or 68Gallium PSMA (prostate specific membrane antigen) scans are changing the ability to diagnose/stage metastatic disease. [Note: **F18 sodium fluoride** is taken up by bone lesions. **F18 Fluciclovine** is a radiolabeled nonnatural occurring amino acid that is taken up by cancer cells due to increased amino acid metabolism for energy and protein synthesis. F18

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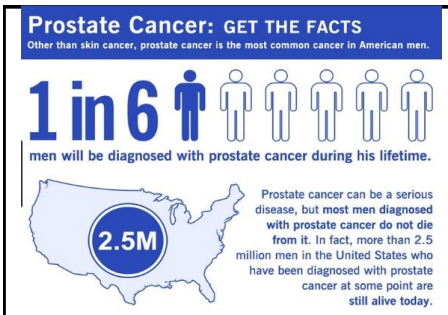

Organization

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 available for purchase on our website at https://ipcsg.org/purchase-dvds and are generally available by the next meeting date.

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** Bill Lewis @ (619) 591-8670 ; or **Director** Gene Van Vleet @ 619-890-8447.

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 broadcast via the IPCSG website at https://ipcsg.org/live-stream and can be watched by scrolling down and clicking on the "WATCH THE PRESENTATION" button. The broadcast will begin approximately 10 minutes before to the listed start time.

In this issue:

Bill Lewis produced a short summary of the last stream video, .

Articles of Interest:

1. Novartis 177Lu-PSMA-617 significantly improves overall survival and radiographic progression-free survival for men with metastatic castration-resistant prostate cancer in Phase III VISION study - targeted radioligand therapy, plus best standard of care (SOC) demonstrated significant improvement in overall survival (OS) compared to SOC alone, in patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
2. Stage 4 Prostate Cancer Prognosis Can Vary by How It Has Spread - While stage 4 prostate cancer isn't usually curable, it is treatable. A combination of several treatments is usually used over time for this stage of the disease
3. Recent Advances in Systematic and Targeted Prostate Biopsies - TRUS biopsy has remained the mainstay of clinical diagnosis because of its simplicity; however, the recent development of simpler local anaesthetic transperineal techniques has transformed outpatient biopsy prac-

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piflufolastat, also known as **Pylarify**, binds to a surface membrane protein that is present – actually, very much overexpressed – on prostate cancer cells anywhere in the body. Likewise, **68Ga PSMA-11** similarly binds to PCa cells.] With these new agents, we can now see much smaller metastases, so the group with an oligometastatic diagnosis is growing rapidly. Such PSMA PET-CT scans before radiation or surgery are becoming a game-changer, so that it may be that the current 30-40% recurrence will be eliminated because those already-metastatic men will have been identified, and not be given surgery or radiation (but instead be given whole body treatment such as hormone therapy and/or chemotherapy). Interestingly, a few other cancers also express PSMA, and a very small percentage of PCa disease does not express it. There may also be PSMA protein on (healthy) lung, salivary gland or kidney cells.

Another group of men with rising PSA, about twenty percent of the total, have one or more of 20-plus genetic defects that can account for their tendency for recurrence after primary treatment. Our increasing ability to identify relevant genetic abnormalities, especially DNA repair mutations, can lead to precision medical treatment using e.g., PARP inhibitors.

Blood and Urine Tests for Prostate Cancer: If the PSA is elevated, since the test is not always accurate, it is important to repeat at the same lab in a few weeks, and also try to get an idea about the doubling time, which indicates aggressiveness if it is short. When there is oligometastatic recurrence (fewer than 5 lesions), it is usually in the bone. Polymetastatic disease often involves many sites and may include soft tissue, bone, organ and/or lymph nodes. A very low PSA may not be of concern especially in the first 8 months after radiation, but after surgery would need attention. Newer liquid biopsies are not yet approved for general use but show future promise. Ultrasensitive PSA testing is available but is expensive and usually not necessary.

Action -- Now what to do? **Intensify treatment early based on PSA and PSMA tests that suggest oligometastatic disease!**

PSMA is the game changer. So many bone scans were negative when the patient already had oligometastatic disease. Recurrent disease usually needs treatment. Exceptions: poor health, other significant illnesses, advanced age.

Treatment: ADT **(**Androgen suppression) – almost all of the newer combinations require suppression of testosterone with injections of Lupron, Firmagon, or the like – or by using the new oral ORGOVYX (relugolix). This latter has many advantages – it is an oral pill, gives very fast suppression of testosterone with no PSA flare, has fewer cardiac side effects, and allows rapid return of natural hormone levels after stopping the pill.

There are second-generation androgen receptor inhibitors and androgen biosynthesis inhibitors that are now often used in conjunction with Lupron, Orgovyx or the like. These include Erleada (apalutamide), Xtandi (enzalutamide), Nubeqa (darolutamide) and Zytiga (abiraterone; usually taken with prednisone). These take treatment to a new level, but side effects need management.

Surprisingly, in cases of denovo oligometastatic disease (i.e., no prior treatment, but initial diagnosis), treatment of the primary prostate lesion with radiation seems to really help; less is known about surgical removal, but that is now also being studied. It seems that the prostate continues to shed tumor cells to spread in more locations. It is also noteworthy that circulating tumor DNA has been found in some men without evidence of a primary prostate cancer.

Immunotherapy can help the immune system fight the cancer. Sipuleucel-T (Provenge) has been available for some time. It is very under-utilized, but may be helpful in combination with other therapies such as Zytiga or chemotherapy.

Chemotherapy has changed the picture in metastatic disease, especially high-volume disease. Docetaxel (Taxotere) and cabazitaxel (Jevtana) have often been very effective with relatively few side effects. PARP inhibitors are especially helpful for men with BRCA2 genetic defects, and for men undergoing combination therapies. See also

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checkpoint inhibitors. Genetic testing – BRCA1, BRCA2, ATM and 20 others are being studied. Two genetic defects, for which testing is not yet commercially available, seem to indicate whether disease under active surveillance is likely to progress or not.

Second Generation Antiandrogens: First generation antiandrogens (Lupron, etc.) do not completely block androgen activity. Second generation antiandrogens include abiraterone acetate (Zytiga), enzalutamide (Xtandi), apalutamide (Erleada) and darolutamide (Nubeqa). Abiraterone inhibits androgen biosynthesis [in testes, adrenal glands AND in PCa cells!], but [usually] needs prednisone to make up for other hormone deficiencies. It is often effective even when other meds aren't working and seems to work well with immunotherapies. The androgen receptor blockers are effective, with a slight risk of seizures (with enzalutamide, apalutamide, and least darolutamide). There are other possible side effects with each of these second-generation drugs, but darolutamide seems to have the least side effects overall.

What To Do? Active surveillance is still a possibility if the PSA is low, especially if life expectancy is under five years due to age and other health problems. After surgical treatment, a rising PSA is often treated effectively with salvage radiation. After radiation treatment, a rising PSA might lead to surgery (difficult due to scar tissue, but done at Stanford), focal therapy (if only one tumor – using HIFU, cryosurgery, laser, or high intensity ultrasound) or a focused second course of radiation. Nearly always, a first-generation antiandrogen is started, and it should be started very early, as part of an "intensification" approach. Many experts recommend adding a second-generation antiandrogen as well, with a growing bias toward darolutamide due to the low side effects. Oligometastatic men survived on average 40 months, vs. 18 months without a second-generation antiandrogen.

There is long-term promise for immunotherapy, use of genetic information and new PARP or check point inhibitors for certain men. Chemotherapy, especially for high volume metastatic PCa really helps, using docetaxel or the newer cabazitaxel.

Advanced disease needs to be under the direction of a Urologic Oncologist or an Oncologist that deals with prostate cancer. Long gone are the days of general community based Urologic care. Most urologists aren't able to adequately deal with the side effects of advanced PCa care. All tertiary centers have Urologic departments with MD's specializing in Prostate Cancer oncology. The City of Hope model of using teams of doctors is one approach [as is UCSD's team approach].

Combination Therapies: Resistance to one antiandrogen usually means there not much hope in switching to others. Chemotherapy may go better with the newer taxanes such as cabazitaxel. The new gold standard for mCSPC (metastatic castrate sensitive prostate cancer) is androgen suppression, taxane chemotherapy and an androgen receptor inhibitor. PARP inhibitors are effective when there are mutations in DNA repair pathways, but also have shown benefit in combination with some other therapies. Theranostics, i.e., use of a radioactive ligand that binds to and kills PCa cells, is relatively new to the western world, but use is sure to grow.

A New Use for PET Fluciclovine and other PET-CT agents: Scan prior to radiation and then give treatment where it's needed. Also useful during surgery to see margins better. Can use theranostics after surgery, or whenever there is a rising PSA for better targeted treatment, to only destroy the cells that have PSMA. Ways to prevent damage of salivary glands and the kidneys (which have PSMA on them), to only kill PCa cells have already been worked out. Besides using 177lutetium attached to a PSMA ligand, there are also studies underway with attached PARP inhibitors or 64copper (lower side effects).

Radiation and Androgen Suppression: Neoadjuvant use of antiandrogens means using them prior and during radiation treatment. Adjuvant use is during and after treatment. The gold standard was before and after, but now is during and after. This is a game changer for radiation patients.

Genetic Testing: 1/3 of practicing urologists do not test! Advanced prostate patients often have abnormalities that can change precision-of-treatment choices. Certain new drugs are indicated in some germline mutations – especially the PARP inhibitors and checkpoint inhibitors.

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What's New in the PCa World: The relugolix (Orgovyx) oral pill is a great advance over injections. PCa enters the PARP era: targeted therapies, specifically for men with specific genetic alterations. Helps block the ability of the protein PARP to repair damaged DNA. As many as 30% of men have this genetic alteration (BRCA1, BRCA2). Survival was twice as long as the control group. The BRCA2 group did the best. Side effects included anemia, low WBC count, nausea and vomiting. ATR inhibitors are another way to stop DNA repair; these are early in studies.

So... what to do?

Very complex process, very much suggest getting to an academic center with a urology-oncology specialist. All these centers have one. The newest advances come with clinical trials. Must have genetic data to move on intelligently. Insurance coverage – must have an advocate if insurance doesn't cover newer treatments. Insurance medical directors do listen to facts, it is their job.

Questions:

A comment: Good results and low side effects with 12 months of Orgovyx replacing Firmagon. Financial assistance is available from the Drug Manufacturer for those that need assistance.

Genetic testing is currently available for no cost from COLOR Program, and will be used for genetic research as well as identification of known mutations associated with PC. Do you recommend this for PCa diagnosed individuals? Sounds like a great opportunity.

Can you address the guidelines for PSMA Scans relative to PSA levels? Is a 0.2 PSA level the minimum for detection with a PSMA scan, and a PSA of 2 is preferred for detection? Although this is currently true, newer PSMA agents already submitted to the FDA will allow good scans at the lower end of this range.

What would cause a rise in PSA level without cancer present? There could be some non-cancerous cells still present and secreting PSA. Or the clusters of PCa cells may be too small to detect, especially if the PSA is quite low. Also, some PCa cells may not express PSMA, so may not be detected.

Can you explain Theranostics? Attaching a lethal radioactive agent to a PSMA ligand, so it is carried to the PCa cells.

2 years after prostatectomy my PSA is rising from 0.02 to 0.06. What should I expect? This might be a great time for a liquid biopsy. Otherwise, use active surveillance until the PSA rises higher [or start hormone suppression].

How common are cardiac problems related to hormone therapy? Probably 8-10%, especially with Lupron. There is an amino acid, glutamine, being studied at Duke University that if blocked may provide similar benefits as androgen deprivation, without the side effects of low testosterone. [see https://corporate.dukehealth.org/news/prostate-cancer-uses-metabolic-switch-thrive-after-hormone-therapy or a list of inhibitors in the book "How to Starve Cancer" by J. McClelland, pp 360-372; summary available from Bill Lewis].

I was diagnosed at stage 4 metastatic to the bone at time of diagnosis. I was on Lupron and abiraterone/prednisone for 2 years. My new Scripps oncologist took me off Lupron saying it was 'duplication' and not needed. I have since (last year) had more intense side effects (bone pain and cardiac issues). Was that incorrect to do? Dr. Metzger would go to Orgovyx, and hopefully avoid cardiac side effects. He feels both (Orgovyx and the Zytiga) are needed for "intensification." He would also use theranostics – which work better in the bones than in soft tissues. For oligometastatic disease, the Germans have had excellent results with theranostics.

My PC returned 5 years ago. PSA had risen slowly to 9.0; doubling time greater than two years. No spread noted on multiple scans with Axumin. Active surveillance only so far. When should I treat it? Dr. Metzger would continue active surveillance until a PSMA scan shows something.

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You mentioned preexisting conditions earlier as a condition for treatments "in older men". At 50 does hypertension, obesity, anemia have an effect on treatment options and effects of treatment? Yes, there would need to be consideration of side effects of treatments. In the past, such cases were treated with removal of the testicles, but that is rare now.

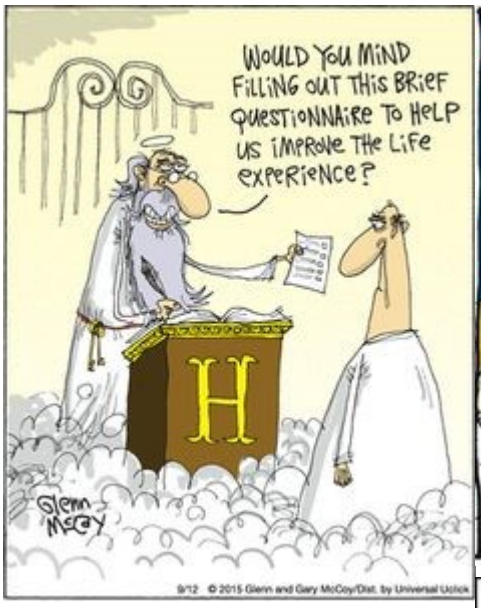
Dr. Metzger: About half the men treated for PCa over the years did not need to be treated. It's an embarrassment to the profession. Active surveillance is appropriate for many men.

Additional questions may be directed to ckmetzger@mac.com

We recommend that you watch the video online for more definitive information about the talk and slides: https://www.youtube.com/watch?v=8c8ydHbvEe8

A DVD of the talk and the slides from Dr. Metzger will be available for purchase from the IPCSG about one month after the meeting.

On the Lighter Side



"Your first week on the job and you're already going to call in sick?"

"We're experimenting with some exciting new employee productivity and retention programs."

.Articles of Interest

globenewswire.com

Novartis 177Lu-PSMA-617 significantly improves overall survival and radiographic progression-free survival for men with metastatic castration-resistant prostate cancer in Phase III VISION study

Novartis Pharma AG

Men who received ^{177}Lu-PSMA-617 plus best standard of care had a 38% reduction in risk of death (median OS benefit of 4 months) and a 60% reduction in the risk of radiographic disease progression or death (median rPFS benefit of 5 months) compared to best standard of care alone[1]

Significant improvement demonstrated in all key secondary endpoints, including time to first symptomatic skeletal event, overall response rate and disease control rate[1]

VISION study findings to be presented during 2021 ASCO plenary; regulatory submissions to US and EU Health Authorities on track for 2H21; two additional pivotal studies in earlier lines of treatment for metastatic prostate cancer to start 1H21, goal to move into earlier stages of disease

Novartis commitment to leadership in radioligand therapy (RLT) further strengthened by recent partnerships and investments; more than 15 ongoing research and discovery programs to identify and accelerate next wave of RLTs for cancer

Basel, June 3, 2021 — Novartis today announced that results of the Phase III VISION study evaluating ^{177}Lu-PSMA-617, a targeted radioligand therapy, plus best standard of care (SOC) demonstrated significant improvement in overall survival (OS) compared to SOC alone, in patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)[1]. The difference in OS between study arms was statistically significant (one-sided p<0.001), with an estimated 38% reduction in risk of death in the ^{177}Lu-PSMA-617 arm (n=551) compared to the best standard of care only arm (n=280) (hazard ratio: 0.62 with 95% confidence interval (CI): (0.52, 0.74))[1]. These results will be presented during the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting plenary session on June 6.

Patients receiving ^{177}Lu-PSMA-617 also demonstrated a statistically significant (one-sided p<0.001) 60% risk reduction for radiographic progression-free survival or death (rPFS), compared to the best standard of care only arm (hazard ratio: 0.40 with 99.2% CI: (0.29 0.57))[1]. There was a higher rate of drug-related treatment emergent adverse events reported in the ^{177}Lu-PSMA-617 treatment arm (85.3%) compared to standard of care alone (28.8%)[1].

Across both arms of the study, rates of treatment discontinuation associated with treatment-emergent adverse events occurred as follows: In the ^{177}Lu-PSMA-617 plus standard of care (SOC) arm, 11.9% of patients discontinued ^{177}Lu-PSMA-617 and 8.5% discontinued SOC; while in the SOC alone arm 7.8% of patients discontinued treatment[1].

"Patients suffering from metastatic CRPC who have progressed through contemporary hormonal treatments and chemotherapy have few meaningful therapeutic options," said Michael J. Morris, MD, who chaired the study's Scientific Committee and is the Prostate Cancer Section Head, Genitourinary Oncology Service, Division of Solid Tumor Oncology at Memorial Sloan Kettering Cancer Center. "The study demonstrated that ^{177}Lu-PSMA-617 improves disease progression and prolongs survival, which are key measures of clinical benefit in the mCRPC population. I am grateful to be a part of this study that may lead to additional therapeutic options for these patients."

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"Men with metastatic prostate cancer have an approximately 3 in 10 chance of surviving 5 years[2]. These data from the first Phase III study of a radioligand therapy in this advanced prostate cancer setting confirm the potential of ^{177}Lu-PSMA-617 targeted therapy to improve clinical outcomes," said John Tsai, Head of Global Drug Development and Chief Medical Officer for Novartis. "Our comprehensive development program for this targeted therapy seeks to reach eligible patients with advanced prostate cancer, who express the PSMA biomarker[1,3-6]. And, we won't stop with prostate cancer, our team is exploring next generation RLT across a number of tumor types."

Two additional studies with ^{177}Lu-PSMA-617 radioligand therapy in earlier lines of treatment for metastatic prostate cancer are planned to start in the first half of 2021, investigating potential clinical utility in the mCRPC pre-taxane setting (PSMAfore) and in the metastatic hormone-sensitive setting (PSMAddition).

Additional VISION data

Median OS (95% CI) for the ^{177}Lu-PSMA-617 plus best standard of care arm in the VISION study was 15.3 months (14.2, 16.9), compared to 11.3 months (9.8, 13.5) in the best standard of care arm only[1]. The median rPFS (99.2% CI) was 8.7 months (7.9, 10.8) for the ^{177}Lu-PSMA-617 arm compared to 3.4 months (2.4, 4.0) for the best standard of care only arm[1].

Key secondary endpoints were also met. The median time to first symptomatic skeletal event was 11.5 months (95% CI: 10.3, 13.2) in ^{177}Lu-PSMA-617 arm compared to 6.8 months (95% CI: 5.2, 8.5) in the best standard of care only arm (hazard ratio: 0.50 (95%CI: 0.40, 0.62)); two-sided p-value: <0.001[1]. Significant differences were also seen in overall response rate in patients with measurable or non-measurable disease at baseline (29.8% partial or complete response in the ^{177}Lu-PSMA-617 arm compared to 1.7% partial response in the best standard of care only arm (two-sided p-value: <0.001)) and disease control rate (89.0% in ^{177}Lu-PSMA-617 arm compared to 66.7% in the best standard of care only arm (two-sided p-value: <0.001))[1].

Grade ≥3 drug-related treatment emergent adverse events occurred in 28.4% of the ^{177}Lu-PSMA-617 arm compared to 3.9% in the best standard of care only arm[1]. The most common treatment emergent adverse events regardless of drug relatedness (above 2% respectively for the ^{177}Lu-PSMA-617 and best standard of care arm) were anemia (12.9% vs. 4.9%), thrombocytopenia (7.9% vs. 1%), lymphopenia (7.8% vs. 0.5%), fatigue (5.9% vs. 1.5%), urinary tract infection (3.8% vs 0.5%), neutropenia (3.4% vs 0.5%), hypertension (3.2% vs 1.5%), back pain (3.2% vs. 3.4%), acute kidney injury (3.0% vs 2.4%), leukopenia (2.5% vs. 0.5%), bone pain (2.5% vs. 2.4%), hematuria (2.5% vs 0.5%), and spinal cord compression (1.3% vs. 5.4%)[1].

Serious drug-related treatment emergent adverse events occurred in 9.3% of patients in the ^{177}Lu-PSMA-617 arm compared to 2.4% in the best standard of care only arm[1].

Visit https://www.hcp.novartis.com/virtual-congress/a-2021/ for the latest information from Novartis, including our commitment to the Oncology community, and access to our ASCO21 Virtual Scientific Program data presentations (for registered participants).

About Advanced Prostate Cancer

Prostate cancer is a form of cancer that develops in the prostate gland, a small walnut shaped gland in the pelvis of men. In castration resistant prostate cancer (CRPC), the tumor shows signs of growth, such as rising Prostate Specific Antigen (PSA) levels, despite the use of hormone treatments that lower testosterone[7]. In metastatic CRPC (mCRPC), the tumor spreads to other parts of the body, such as neighboring organs or bones and remains unresponsive to hormone treatment[7]. The five-year survival rate for patients with metastatic prostate cancer is approximately 30%[2].

About Phenotypic Precision Medicine in Advanced Prostate Cancer

Despite advances in prostate cancer care, there is a high unmet need for new targeted treatment options to improve outcomes for patients with mCRPC. More than 80% of prostate cancer tumors highly express a phenotypic biomarker[6] called Prostate Specific Membrane Antigen (PSMA) [3-5,8-9], making it a promising diagnostic (through posi-

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tron emission tomography (PET) scan imaging) and potential therapeutic target for radioligand therapy[10]. This differs from 'genotypic' precision medicine which targets specific genetic alterations in cancer cells[6].

About ^{177}Lu-PSMA-617

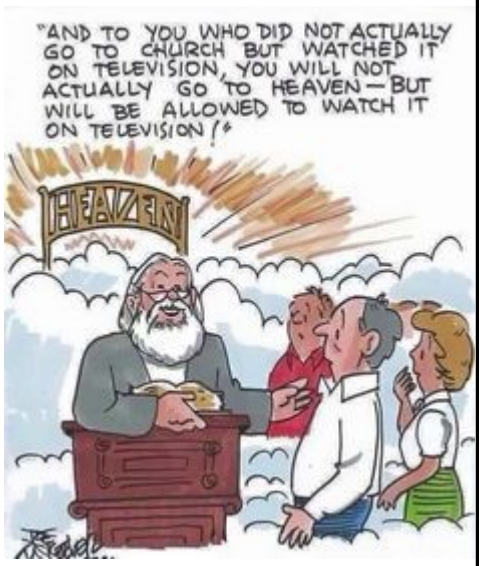
^{177}Lu-PSMA-617 is an investigational PSMA-targeted radioligand therapy for metastatic castration-resistant prostate cancer. It is a type of precision cancer treatment combining a targeting compound (ligand) with a therapeutic radioisotope (a radioactive particle)[11-13]. After administration into the bloodstream, ^{177}Lu-PSMA-617 binds to prostate cancer cells that express PSMA[14], a transmembrane protein, with high tumor-to-normal tissue uptake[11,15,16]. Once bound, emissions from the radioisotope damage tumor cells, disrupting their ability to replicate and/or triggering cell death[17-19]. The radiation from the radioisotope works over very short distances to limit damage to surrounding cells[10,11,15].

About VISION

VISION is an international, prospective, randomized, open-label, multicenter, phase III study to assess the efficacy and safety of ^{177}Lu-PSMA-617 (7.4 GBq administered by intravenous infusion every 6 weeks for a maximum of 6 cycles) plus investigator-chosen best standard of care in the investigational arm, versus best standard of care in the control arm[20]. Patients with PSMA PET-scan positive mCRPC, and progression after prior taxane and androgen receptor pathway inhibitors, were randomized in a 2:1 ratio in favor of the investigational arm[20]. The alternate primary endpoints were rPFS and OS[20]. The study enrolled 831 patients[1].

On the Lighter Side

"It's a flashlight. I couldn't find any candles."



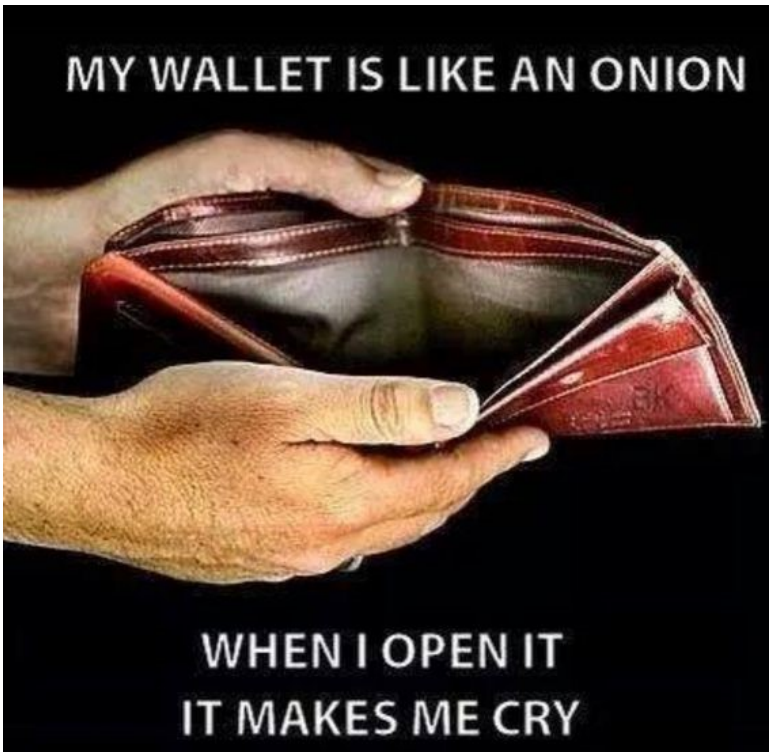
NETWORKING

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

Member 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.

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

Editors Notes, Continued from Page 2

tice.

4. Prostate Cancer Survival Rates By the Numbers: Diagnosis and Survival - The 5-year survival rate in the United States for men diagnosed with early-stage prostate cancer is greater than 99%.
5. Prostate cancer urine test identifies good prognosis patients -this non-invasive PUR test may be able to support decision-making process without needing an invasive prostate biopsy
6. Use of PSMA PET Scans in Advanced Prostate Cancer - a more informed conversation with patients regarding considerations for active surveillance, immediate active treatment of the prostate, of the primary organ, whether it's surgical or radiation, as well as possibilities for systemic therapy or just systemic therapy as the ideal therapy
7. What Treatments are Used for Prostate Cancer? Good overview by Dr. Scholz.
8. AUA 2021: State-of-the-art Lecture: Personalized Medicine in the Management of Prostate Cancer— assessing a patient on a number of factors (clinical features, genetics, genomics, serum markers, receptors, induced responses, and selection pressures) and then developing a personalized approach to their treatment plan .
9. Certain Types of Cancer May Increase the Risk of Developing Guillain-Barré *prostate cancer had a five-and-a half times greater risk*
10. Metastatic prostate cancer on the rise since decrease in cancer screenings -the incidence rate of metastatic prostate cancer has significantly increased for men 45 and older and coincides with recommendations against routine prostate cancer screenings
11. 177Lu-PSMA radioligand therapy effectiveness in metastatic castration-resistant prostate cancer: An updated systematic review and meta-analysis -PRLT results in higher proportion of patients responding to therapy based on ≥50% PSA decline compared to controls
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15. Evaluation of selective bone scan staging in prostate cancer –
16. As Predicted: Jump in Metastatic Prostate Cancer Diagnoses - screening practices have already changed
17. Assessment after focal therapy what is the latest? -need better monitoring
18. Implications of DNA damage repair alterations for the management of prostate cancer
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Stage 4 Prostate Cancer Prognosis Can Vary by How It Has Spread

Matthew Schmitz, MD

Stage 4 prostate cancer is the most advanced stage of the disease. It means that cancer has spread beyond the prostate to distant areas of the body. Learn more about this stae, what treatments are available, and the prognosis.

Brianna Gilmartin / Verywell

Understanding Staging

The most common staging system used with prostate cancer is the TNM staging system. Another system used by some hospitals and healthcare providers is the Jewett staging system which breaks down tumors into stage A to stage D.1

With the TNM system, letters stand for:

T is for tumor size.

N is for lymph node involvement. N0 means cancer has not spread to any lymph nodes. N1 means the tumor has spread to nearby lymph nodes. N2 means the tumor has spread to distant lymph nodes.

M is for metastases. M0 means that a prostate cancer has not spread to distant organs. M1 means that a prostate cancer has spread to distant organs—the bones are the most common area of prostate cancer metastases.2

Prostate cancer is considered stage 4 in three different ways:3

A T4 tumor with no lymph node involvement and no metastases.

Any size tumor along with nearby lymph nodes positive (N1) and no metastases.

Any size tumor alone with any lymph node status (none, nearby nodes positive, or distant nodes positive) plus metastases to another region of the body (M1).

Symptoms

Symptoms of stage 4 prostate cancer can be related to cancer in your prostate, or due to metastases. Some of these include:4

Blood in the urine

Difficulty passing urine

Erectile dysfunction

Bone pain from bone metastases

Pain or swelling in the legs or bladder problems

Diagnosis

Tests to diagnose prostate cancer may include a computerized tomography (CT) scan, ultrasound, magnetic resonance imaging (MRI), or positron emission tomography (PET) scan to evaluate the growth and look for metastases. A biopsy is usually done to look at the aggressiveness of the tumor.5

Treatment

While stage 4 prostate cancer isn't usually curable, it is treatable. A combination of several treatments is usually used over time for this stage of the disease.**6**

Hormone Therapy

Hormone therapy is often the mainstay for stage 4 disease. Different options are available to reduce the amount of testosterone in your body. Some medications stop the production of testosterone, and others work to prevent testosterone from stimulating prostate cancer cells.

Just as estrogen works as a fuel to stimulate the growth of many breast cancer cells, testosterone works as a fuel to facilitate the growth of prostate cancer cells.7

Palliative Surgery

A transurethral resection of the prostate (TURP) procedure is sometimes done at this stage. Since stage 4 prostate cancer has by definition spread to other parts of the body, surgery to remove the prostate is not effective in "curing" cancer as it may be in earlier stages of prostate cancer.

These surgeries are sometimes done for symptoms related to the prostate. Sometimes an orchiectomy (removal of the testicles) is also done as a form of hormonal therapy.8

Palliative Radiation

Radiation may be used along with hormonal therapy initially to control pain, and after hormonal therapy has stopped working. Radiation may also be used for bone metastases to decrease pain.9

Treatment of Bone Metastases

Treatment of bone metastases can include a combination of radiation therapy and a medication category called bisphosphonates.10

Chemotherapy

Chemotherapy may work to extend life for men with prostate cancer and also relieve pain due to metastases.11

The prognosis of stage 4 disease varies considerably depending on how far cancer has spread. This can be done by breaking stage 4 down into two parts.

Stage 4 with regional metastases: Prostate cancer that is called stage 4 due to a large tumor size (T4) or due to spread to nearby lymph nodes has a five-year survival rate of nearly 100%.

Stage 4 with distant metastases: According to the National Cancer Institute's SEER data, people who have stage 4 prostate cancer with spread to distant lymph nodes (N2) or to other regions of the body such as bones, had a five-year survival rate of 30.2%.12

Keep in mind that treatments for advanced cancers are improving each year. Every person is different, and clinical trials today may change those numbers tomorrow.

Coping

Learn about your cancer. Be aware of some common prostate cancer emergencies so you can be prepared. Accept help. Stage 4 prostate cancer can sometimes cause significant pain. Talk to your healthcare provider and don't try to be "a hero" and avoid treating your symptoms.

Consider joining a support group or check into online stage 4 prostate cancer communities. If it is your loved one coping with prostate cancer, learn important tips on supporting a loved one with prostate cancer.

Thanks for your feedback!

Verywell Health uses only high-quality sources, including peer-reviewed studies, to support the facts within our articles. Read our editorial process to learn more about how we fact-check and keep our content accurate, reliable, and trustworthy.

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Recent Advances in Systematic and Targeted Prostate Biopsies

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Abstract: Prostate biopsy is the definitive investigation to diagnose prostate cancer. The ideal procedure would be one that offers fast and efficient results safely as an outpatient procedure. Historically, transrectal ultrasound (TRUS) biopsy is considered the gold standard but transrectal biopsy can under-sample the anterior and apical regions of the prostate and is associated with a risk of prostate biopsy-related sepsis, which may require intensive care admission. Transperineal (TP) biopsy addresses the inefficient sampling of TRUS biopsy but historically has

been done under general anaesthetic, which makes it difficult to incorporate into timed diagnostic pathways such as the National Health Service (NHS) 2-week cancer pathway.

TRUS biopsy has remained the mainstay of clinical diagnosis because of its simplicity; however, the recent development of simpler local anaesthetic transperineal techniques has transformed outpatient biopsy practice. These techniques practically eliminate prostate biopsy-related sepsis, have a shallow learning curve and offer effective sampling of all areas of the prostate in an outpatient setting. The effectiveness of TP biopsy has been enhanced by the introduction of multiparametric MRI prior to biopsy, the use of PSA density for risk stratification in equivocal cases and combined with more efficient targeted and systematic biopsies techniques, such as the Ginsburg Protocol, has improved the tolerability and diagnostic yield of local anaesthetic TP biopsies, reducing the risk of complications from the oversampling associated with transperineal template mapping biopsies. Areas where the literature remains unclear is the optimum number of cores needed to detect clinically significant disease (CSD) in patients with a definable lesion on MRI, in particular, whether there is a need for systematic biopsy in the face of equivocal MRI findings to ensure no CSD is missed. The Covid-19 pandemic has had a profound impact on prostate cancer referrals and prostate biopsy techniques within the UK; prior to the pandemic 65% of all prostate biopsies were TRUS, since the pandemic the proportions have reversed such that now over 65% of all prostate biopsies in the NHS are transperineal.

pcf.org

Prostate Cancer Survival Rates By the Numbers: Diagnosis and Survival

Prostate cancer is the most commonly diagnosed type of cancer in the US (excluding skin cancer), and the second leading cause of cancer in men worldwide. 1 in 8 US men will be diagnosed with prostate cancer at some point in their lives. Prostate cancer incidence increases with age: the older you are, the greater your chance of developing it.

Although only about 1 in 451 men under age 50 will be diagnosed, the rate shoots up to 1 in 55 for ages 50 to 59, 1 in 20 for ages 60 to 69, and 1 in 12 for men 70 and older. Nearly 60% of all prostate cancers are diagnosed in men over the age of 65.

Prostate cancer is diagnosed with a biopsy. The most common reason for a man to undergo a prostate biopsy is due to an elevated prostate-specific antigen level (PSA), determined by a blood test. In the last decade, changes in PSA screening recommendations have affected the rates of prostate cancer diagnosis.

While prostate cancer is relatively common, the good news is that about 90% of all prostate cancers are detected when the cancer is confined to the prostate or the region around it, and treatment success rates are high compared with many other types of cancer.

The 5-year survival rate in the United States for men diagnosed with early-stage prostate cancer is greater than 99%. In other words, the chance of a man dying from his prostate cancer is generally low. However, prostate cancer comes in many forms, and some men can have aggressive prostate cancer even when it appears to be confined to the prostate.

Amidst so much optimism and progress in the last 10 years, it's important to keep in mind that prostate cancer is still a deadly disease for some men, and it is the second leading cause of cancer death among men in the US, with 94 men dying from it every day.

In general, the earlier the cancer is caught and treated, the more likely the patient will remain disease-free. In fact, many men with "low-risk" tumors (which are the most common type of prostate cancer), as well as some men with intermediate-risk disease, can safely undergo active surveillance. This means patients are closely monitored without immediate treatment (or treatment-related side effects), while still preserving their chance of long-term survival if the cancer becomes aggressive enough to require treatment.

https://www.pcf.org/about-prostate-cancer/what-is-prostate-cancer/prostate-cancer-survival-rates/

medicalxpress.com

Prostate cancer urine test identifies good prognosis patients

Science X staff

Researchers at the University of East Anglia have shown that a prostate cancer urine test can identify men at 'intermediate risk' who can safely avoid immediate treatment and benefit from 'active surveillance' instead.

A new pilot study published today reveals how urine biomarkers can show the amount of significant cancer in a prostate, highlighting with more certainty which men need treatment.

Previously, the team's Prostate Urine Risk (PUR) test could identify men with high and low risk cancers.

But thanks to some fine-tuning, it can now help men with intermediate-risk disease—for whom treatment options had been less clear.

Prostate cancer is the most common cancer in men in the UK. It usually develops slowly and the majority of cancers will not require treatment in a man's lifetime.

The most commonly-used tests for prostate cancer include blood tests, a physical examination known as a digital rectal examination (DRE), an MRI scan and an invasive biopsy.

However, doctors struggle to predict which tumors will progress to a more aggressive form, making it hard to decide on treatment for many men.

Lead researcher Dr. Jeremy Clark, from UEA's Norwich Medical School, said: "While prostate cancer is responsible for a large proportion of all male cancer deaths, it is more commonly a disease men die with rather than from.

"Therefore, there is a desperate need for improvements in diagnosing and predicting outcomes for prostate cancer patients to minimize over-diagnosis and overtreatment whilst appropriately treating men with aggressive disease, especially if this can be done without taking an invasive biopsy.

"Here at UEA, we have developed a urine test for prostate cancer called the Prostate Urine Risk Test—or PUR for short.

"The 'risk' here refers to the aggressiveness of the cancer and its potential to spread to other organs, which would eventually kill the patient. But prostate cancer is very complex and risk levels vary widely between men.

"Previously we have shown that PUR can identify men with high-risk cancer which requires immediate treatment and also low-risk cancer that has a very low rate of progression and does not generally need treatment.

"But there is a third category of men with 'intermediate-risk', which falls in between these extremes. Around half of men diagnosed with prostate cancer fall into this group and the treatment pathways for them have been less clear, until now.

"It is known that disease progression in intermediate-risk men is associated with the presence of increasing amounts of Gleason pattern 4 cancer in their prostate. Our study shows that the PUR test can assess the amount of Gleason pattern 4 without the need for a biopsy.

"So not only can PUR measure the presence of aggressive cancer, but it can also measure increasing amounts of aggressive cancer in a prostate.

"This means that it can show us which men at intermediate risk may require treatment and which may instead be managed conservatively with surveillance.

"PUR will also be useful for monitoring disease in men that do not currently require treatment, and flag up the emergence and expansion of aggressive disease," he added.

The results of this pilot study will be further investigated in a much larger cohort of men using samples collected with a prostate screening box which the patients receive by mail and return samples by post directly for analysis at UEA.

Prof Daniel Brewer, also from UEA's Norwich Medical School and a visiting worker at the Earlham Institute, said: "Prof Dan Brewer, also from UEA's Norwich Medical School and a visiting worker at the Earlham Institute, said: "We have recently developed a urine biomarker test for prostate cancer named PUR that can distinguish whether men should be placed on active surveillance or have radical treatment.

"In this research we examine in more detail what biological change PUR is detecting. This is an exciting finding that helps explain why PUR works so well.

"This test is currently being validated in a large multiple site study supported by Prostate Cancer UK and Movember," he added.

Dr. Sarah Hsiao, Director, Biomedical Research and Impact at Movember, said: "This new research from Dr. Clark's team shows that the PUR test can be used to estimate the level of a specific pathological characteristic (Gleason Pattern 4) that is linked to increased risk of disease progression in men with prostate cancer.

"This is important because, for men whose prostate tumor contains varying levels of Gleason Pattern 4, a prostate biopsy is necessary to determine whether men should receive active treatment or be managed by active surveillance.

"We look forward to seeing further validation of this research in a larger study cohort. If successful, this non-invasive PUR test may be able to support decision-making process without needing an invasive prostate biopsy that is associated with discomfort and risk of infection."

This study was led by UEA in collaboration with researchers in the Urology and Cellular Pathology departments at the Norfolk and Norwich University Hospital, Hull University Teaching Hospitals NHS Trust, the Institute of Cancer Research, The Royal Marsden, and the Earlham Institute.

"The Urine Biomarker PUR-4 is Positively Associated with the Amount of Gleason 4 in Human Prostate Cancers" is published in the journal *Life* (MDPI) on November 3, 2021.

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onclive.com

Use of PSMA PET Scans in Advanced Prostate Cancer

Neal Shore, MD, Carolina Urologic Research Center

Neal Shore, MD: When looking at PSMA [prostate-specific membrane antigen] as a PET [positron emission tomography], as that radiotracer, we have 2 very exciting applications that have different approvals throughout the world. In the United States, we have the approval of Gallium 68 PSMA-11 PET at 2 centers in California, and most recently in May, the FDA approved 18F-DCFPyL, or PYLARIFY, as another PSMA PET tracer. Our colleagues in Germany and Australia have had these for quite some time, and there are areas in Northern Europe and in Latin America that have had the ability to use PSMA PET.

Historically, based on the assessments from Prostate Cancer Clinical Trials Working Group [PCWG] 1, 2, and 3, we've used conventional imaging in our global, randomized prospective trials when evaluating disease assessment baseline, and also progression when interrogating a new therapeutic. The PCWG has used—and still to this day—conventional imaging, which is multi-slice CT scan and technetium bone scan. We've had other PET technologies

over the years, such as sodium fluoride and fluciclovine, which has a lot of utilization in the United States; it's known as the Axumin scan.

The addition of the PSMA PET scans will create a much more robust ability to identify disease when newly diagnosed. There may be high risk for localized expansion outside the prostate or extension: extra prostatic involvement, nodal involvement, and bone disease involvement that until now we could not evaluate with conventional imaging. Why does this make a difference? It can impact our abilities to have a more informed conversation with patients regarding considerations for active surveillance, immediate active treatment of the prostate, of the primary organ, whether it's surgical or radiation, as well as possibilities for systemic therapy or just systemic therapy as the ideal therapy. We're in the learning arena right now. We have to do many more trials to understand how this information of more accurate low-volume disease identification compares with how we've done our trials with conventional imaging over the years.

TRANSCRIPT EDITED FOR CLARITY

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What Treatments are Used for Prostate Cancer?

Mark Scholz, MD

The treatment options for prostate cancer can vary based on many factors, including the aggressiveness of the tumor, the stage of the disease, personal preferences, and more. Curative options may include surgery or radiation therapy. With less aggressive tumors, watchful waiting (active surveillance) with treatment begun only if the cancer progresses may be an option. There are also a number of different therapies that can be used to control the growth of these cancers, including hormone therapies, chemotherapy, and newer treatments such as immunotherapy. In addition, many alternative treatments are being evaluated in clinical trials.

IMM-GARO/PHANIE/Getty Images

Understanding Your Options

Many prostate cancers are non-aggressive, and if, left alone, would not pose a problem over the long term. With these tumors, observing the tumor (active surveillance) and treating the tumor only if it shows signs of progressing may be an option.

With early prostate cancers that show signs of being aggressive, and in people who are able to tolerate treatments such as surgery, the aim of therapy is usually a cure. Surgery and radiation are considered standard treatment options, though alternatives—such as proton therapy, cryoablation, and high intensity focused ultrasound—are being evaluated.1

With more advanced prostate cancers (including metastatic tumors), or in those who are unable to tolerate curative treatments, the aim is usually to control the growth of the cancer for as long as possible. Systemic treatments may include hormonal therapies, chemotherapy, immunotherapy, or a clinical trial. Keep in mind that, unlike many cancers, advanced prostate cancer can often be controlled for a long period of time with these treatments (often decades).2

Knowing whether your cancer is low-grade, intermittent-grade, or high-grade is critical in making the best choices about treatment.

Many men are more likely to die *with* prostate cancer than *from* prostate cancer, and in many cases, the goal is to treat the disease while preserving the best quality of life.3

Active Surveillance

Active surveillance is often referred to as watchful waiting, though some use these terms to describe slightly different approaches.4

With **active surveillance**, a man chooses not to have his cancer actively treated *at the current time.* PSA levels are checked at specific intervals (for example, every six months), with a digital rectal exam performed yearly, and second and third biopsies done six to 12 months and two to five years after beginning surveillance. (The timing can vary depending on characteristics of the cancer.) If at any time the cancer appears to progress, active treatment is then started.

Active surveillance is most often used with early-stage, slow-growing tumors, for which the side effects of treatment (such as erectile dysfunction and incontinence) outweigh the potential benefits of treatment.

It is used most often with Gleason 6 tumors, but may also be used for men with tumors that have higher Gleason scores who may decide the side effects of treatment outweigh benefits for personal reasons, or due to other health conditions.

It's extremely important to note that active surveillance is viewed as a standard treatment method by many of the cancer organizations. It's thought that around a third of men who are "treated" with active surveillance will require active treatment at some point in the future, but waiting to see if a person falls in that category does not carry the risk of the disease suddenly metastasizing and causing death.

When a physician makes a distinction between this and **watchful waiting**, he or she is typically using the latter term to refer to a similar approach with no or less frequent testing. This may be an option for treatment for those who are expected to live less than five years, for example. In this case, follow-up tests are not usually done unless symptoms develop, and if this occurs, treatment may be initiated at that time. There are a number of other reasons why this option may be chosen as well.

Surgery

Surgery can help cure prostate cancer if it hasn't spread beyond the prostate gland. Radiation can also be curative. Other surgical procedures may be used for other reasons, such as symptom control.

Prostatectomy

In a **traditional prostatectomy**, an incision is made midline in the abdomen, between the belly button (umbilicus) and pubic bone. A surgeon uses this access point to manually remove the prostate gland as well as surrounding tissues, such as the seminal vesicles. In a **radical retropubic prostatectomy**, pelvic lymph nodes may be removed as well.5

Surgeons can also achieve this treatment goal with what's known as a **robotic prostatectomy**. Instruments are inserted into several small incisions in the lower abdomen, which are moved by a robot controlled by a surgeon rather than the surgeon's hands themselves.

This is less invasive than the manual procedure, gives the surgeon better visibility, and may have several other advantages, including less of a risk of blood loss, shorter recovery time, and faster removal of the catheter (one is required for either procedure).

Robotic prostatectomy is a highly specialized procedure, and there is a steep learning curve in learning the technique. For those who choose this option, you must find a surgeon specially trained to perform the procedure and has a significant level of experience in doing so.

The risk of sexual side effects as well as incontinence is similar among the above options.5

After the surgery is performed, the prostate tissue is sent to a pathologist to determine if all of the tumor was removed. With prostate cancer, this can be challenging. The rectum and bladder lie within millimeters of the prostate gland and cannot be removed with surgery. This means that sometimes a surgeon will cut through a tumor rather than around the tumor, leaving prostate cancer cells behind.

When cancer cells are left behind (when **surgical margins** are positive) the risk of the cancer recurring is around 50%. Further treatment will depend upon the aggressiveness of the tumor but may include careful monitoring, radiation treatment to the prostate fossa, hormonal therapy, and/or chemotherapy.

Transurethral Resection of the Prostate (TURP)

In this procedure, a resectoscope is inserted in the urethra, and an electrically activated wire loop is used to burn away prostate tissue.

A TURP is not done as a curative treatment for prostate cancer. It is sometimes recommended as a palliative procedure (to help symptoms but not cure the disease) for stage 4 cases. It may also be done to treat BPH (benign prostatic hyperplasia) with symptoms that persist despite treatment.5

Orchiectomy

An orchiectomy is the surgical removal of both of the testicles. Since the testicles produce 95% of the testosterone in the body, this procedure greatly reduces the amount of the testosterone in the body. (Just as normal prostate cells are driven by testosterone, the hormone acts as the fuel that drives the growth of prostate cancer cells.)

Post-Operative Care

After a prostatectomy (either manual or robotic) men will have a Foley catheter in place. The catheter will usually be left in place for at least 24 hours but may need to remain in place for up to two weeks while swelling and inflammation resolves. During the first few days, it's normal to pass some blood or small clots. Your surgeon will instruct you in good incision care following discharge, which can reduce your risk of infection or other complications.

In general, men can return to their normal activities within four weeks of surgery but may be able to do so in as little as a week following outpatient procedures.

As with any surgical procedure, there is a risk of side effects and complications following a prostatectomy. Possible complications, which may be temporary, include the following. Most men do not experience all of these:5

Difficulty urinating

Urinary incontinence, though there are a number of treatments that can help this

Bleeding

Infection

Erectile dysfunction

Retrograde ejaculation (ejaculation into the bladder rather than out of the penis)

Surgical injury to structures surrounding the prostate

TURP syndrome, an uncommon but potentially serious complication of TURP surgery that results from a serious drop in serum sodium due to flushing of fluids during the procedure

A change in penis size (With a radical prostatectomy, roughly 20% of men will note a change in size or girth of the penis of 15% or more.)

Radiation Therapy

Radiation works by using high energy rays to damage and kill cancer cells and may be used as the primary treatment for prostate cancer as an alternative to surgery (curative therapy); after surgery as an adjuvant therapy to treat any remaining cancer cells that remain; or as a palliative treatment to improve symptoms, but not to cure the cancer.6 Radiation can be very helpful to treat areas of bone metastases due to the disease.

Radiation therapy may be given externally or internally, and oftentimes the two methods are used together.

External Beam Radiation Therapy

In this procedure, you are positioned on an exam table and radiation is delivered through the outside of the body and focused on the prostate gland and surrounding tissue. A gel called SpaceOAR may be placed between the rectum and prostate to reduce the risk of rectal burns, but techniques for delivering radiation have improved remarkably in recent years and cause much less damage to surrounding normal tissues than in the past.6

Brachytherapy (Radioactive Seed Placement)

Internal radiation therapy, also known as brachytherapy, radioactive seed placement, or simply "seed implant," may be used as the primary treatment for prostate cancer in the early stages, or in combination with external radiation therapy when there's an increased risk of cancer spreading beyond the prostate. In this procedure, small seeds or pellets of radiation are implanted in a tumor. Radioactive seeds may be either temporary or permanent.

Traditional brachytherapy is used mostly for low-grade or slow-growing tumors. For men with low to intermediate risk prostate cancer, low-dose brachytherapy may be used alone as the primary treatment for prostate cancer according to 2017 joint guidelines of the American Society of Clinical Oncology and Cancer Care Ontario.

High-dose brachytherapy (HDR) is often used for more advanced tumors. In HDR, a catheter is placed into the prostate between the scrotum and anus, and a needle containing the rice-sized radioactive seeds is then placed inside the catheter and kept in place for five to fifteen minutes. Generally one to four treatments are given over two days.6

When used as a curative therapy, radioactive seed implantation results in higher cure rates than standard beam radiation. In combination, these treatments appear to lower the risk of relapse at nine years post-treatment by 20%, relative to men who have external beam radiation alone. It's thought that for men with intermediate- or high-risk prostate cancer who choose external beam radiation therapy, either a low-dose or high-dose brachytherapy boost should be offered.7

Brachytherapy is not as effective in men who have an enlarged prostate gland.

Side Effects

Side effects of both forms of radiation may include painful urination, frequency, and urgency; incontinence; loose stools; bleeding or pain when passing stools. These symptoms are usually mild to moderate and improve over time. Erectile dysfunction may occur but is more often seen in older men with this pre-existing issue. When it occurs in others, it tends to resolve quickly and completely after treatment.

With external radiation, redness, a rash, and blisters may form on the skin overlying the prostate.

When radioactive seeds are left in place in brachytherapy, cautions are needed as others who are nearby may be affected by the radiation. Men are usually instructed to stay away from pregnant women or small children,6 sometimes for a significant period of time. It's also important to note that the radiation may be strong enough to be picked up at airport screening.

Other Local Therapies

In addition to surgery and radiation therapy, there are a few other local treatments that may be used with a curative intent.

Proton Beam Therapy

Proton beam therapy is similar to conventional radiation therapy in that it uses high energy to destroy cancer cells. However, the rays—which are composed of accelerated protons, or positive particles—pass through tissue directly to a tumor and stop, as opposed to continuing on past the prostate gland where they can damage normal tissue (as is the case with regular radiation).

Proton therapy appears to about as effective as traditional radiation but is thought to cause less damage to normal, healthy cells.

Proton therapy is relatively new compared with some other treatments, and its role as primary therapy (monotherapy) for prostate cancer is promising but still unclear.6

Cryosurgery

Cryosurgery or cryoablation is a technique in which argon and helium are used to freeze the prostate. It is used in the operating room while men are under anesthesia.

Used less than other treatments, cryotherapy can only be used on tumors that are contained within the prostate gland and only present in one location. It may also be used after failed radiation treatment.8

The positive benefits may include a more rapid recovery and shorter hospital stay than surgery (prostatectomy), although the technique carries a greater risk of erectile dysfunction.

High-Intensity Focused Ultrasound (HIFU)

High-intensity focused ultrasound (HIFU) uses ultrasound to generate heat and kill cancer cells. It's thought that HIFU may be less effective than other common treatments, but surgery or radiation therapy may be subsequently used if it is not successful.

Hormone Therapy

Medications can be used to reduce the amount of testosterone present in the body (just like orchiectomy) or interfere with the ability of testosterone to act on prostate cancer cells.

Hormone therapy (androgen deprivation therapy) does not cure prostate cancer but is a mainstay for controlling its growth—sometimes for an extended period of time.

Hormone therapy can be used for men who would otherwise not tolerate other treatments. It can also be used before radiation, to reduce the size of a prostate cancer and make it easier to treat (neoadjuvant therapy), or after, to help "clean up" any remaining cancer cells to reduce the risk of recurrence or relapse (adjuvant therapy). Finally, it can be used for men who have prostate cancers that have recurred after primary treatment or who have cancers that have metastasized (spread) to other regions of the body.9

LH-RH Therapy

Luteinizing releasing hormone (LH-RH) **analogues or agonists** block the signal that tells the testicles to make testosterone, reducing overall production. These drugs are a medical version of an orchiectomy, and the treatment is sometimes referred to as medical castration.9 In contrast to orchiectomy, however, treatment is reversible.

Drugs in this category include:

Lupron (leuprolide)

Zoladex (gosrelin)

Trelstar (triptorelin)

Vantas (histrelin)

When LH-RH agonists are first used, they often cause an *increase* in testosterone levels. To counteract this effect, and anti-androgen medication is often used during the first weeks of treatment.

LH-RH **antagonists** also reduce the production of testosterone by the testicles but do so more rapidly than LH-RH agonists.

Drugs in this category include:

Firmagon (degarelix)

CYP17 Inhibitors

Unlike LH-RH agonists and antagonists, CYP17 inhibitors interfere with the production of testosterone by the adrenal glands (small endocrine glands that sit atop the kidneys). They do so by blocking the enzyme CYP17, which is needed in the reaction that produces androgens.

There is one drug in this category that is approved for use in the United States.9

Zytiga (abiraterone)

There are others (such as orteronel, galeterone, VT-464) that are in clinical trials and more in development. Ketoconazole, an antifungal with CYP17 inhibitory properties, is sometimes used off-label for prostate cancer.

Zytiga (abiraterone) is used along with the medications discussed above to block the production of all testosterone in the body and is used primarily in advanced/high-risk and metastatic prostate cancer. Side effects are usually mild and include problems with potassium levels in the blood. It is sometimes given along with prednisone to reduce these problems, but corticosteroids like prednisone. The medication also enhances the effect of some cholesterol-lowering medications.

Anti-Androgen Therapy

Some anti-androgen medications bind to the androgen receptor on prostate cancer cells so that testosterone cannot, preventing cell division and growth.

These include:

Eulexin (flutamide)

Casodex (bicalutamide)

Nilandron (nilutamide)

Others block the signal from the receptor to the nucleus of the cell, achieving the same result.

While not often used by themselves in the United States, these include:

Xtandi (enzalutamide)

Earleada (apalutamide)

Benign Prostatic Hypertrophy (BPH) Medications

The medications Avodart (dutasteride) and Proscar (finasteride) block dihydrotestosterone.

Avodart or Proscar may be used in prostate cancer:

For men with Gleason 6 tumors to suppress tumors or cause them to regress

Along with Lupron or Casodex to make these drugs work better

To help maintain men on active surveillance and reduce the risk they will need surgery or radiation

When used for men who do not have prostate cancer, these drugs appear to reduce the risk of developing the disease, though there is an increased incidence of high-grade cases in those who do end up diagnosed.

Side Effects and Considerations

Most of the side effects related to hormone therapy are secondary to the reduction of testosterone in the body. It's important to note that one's physical appearance does not change due to these treatments, nor does the voice change.

Side effects of hormone therapy may include:9

Hot flashes

Erectile dysfunction

Decreased sex drive

Breast enlargement (gynecomastia)

Fatigue

Weight gain

Reduced muscle strength

Reduced bone density (osteopenia and osteoporosis)

To reduce these side effects, hormone therapy may sometimes be used intermittently, with breaks from the drug to improve quality of life.

Since testosterone "feeds" prostate cancer, some people have wondered whether men with prostate cancer can take testosterone; replacement hormone can help low sex drive, erection issues, fatigue, and more. Many people would quickly say "no," but there are some situations in which this is possible:

With low-grade or benign tumors (the types that would never spread such as Gleason 6 tumors)

For men who have had surgery or radiation therapy and are felt to be cured, after a waiting period of two to five years

For men who have relapsed after surgery or radiation who are receiving intermittent Lupron, though experts' opinions are divided

For men with prostate cancer who have very severe weakness or muscle loss; the risks of not treating with testosterone may outweigh the risk of the cancer growing.

Chemotherapy

Chemotherapy drugs work by killing rapidly dividing cells such as cancer cells, although normal cells can also be affected. Chemotherapy may both extend life and reduce symptoms for men living with prostate cancer. That said, it cannot cure the disease.

Chemotherapy drugs used for prostate cancer include:10

Taxotere (docetaxel), usually the first-choice chemotherapy drug

Jevtana (cabazitaxel), an enhanced form of chemotherapy that can be used in men who become resistant to Taxotere

Novantrone (mitoxantrone)

Emcyt (estramustine)

Chemotherapy is usually used for prostate cancers that have spread beyond the prostate gland and are no longer responding to the hormonal therapy drugs, but this is changing.10

A 2015 study published in *The New England Journal of Medicine* found that men who had hormone-sensitive tumors and were treated with Taxotere and Lupron survived much longer than men who were treated with Lupron alone. Due to these findings, chemotherapy is now recommended earlier, prior to the development of hormonal resistance for men with significant metastatic disease.

Side Effects

Some of the common side effects of chemotherapy include:10

Hair loss

Bone marrow suppression: This can include a low white blood cell count (chemotherapy-induced neutropenia), a low red blood cell count (chemotherapy-induced anemia), and a low platelet count (thrombocytopenia).

Peripheral neuropathy: Numbness, tingling, and pain in the hands and feet are common, especially with drugs such as Taxotere and Jevtana. While most of the side effects of chemotherapy resolve shortly after treatments are completed, peripheral neuropathy may persist.

Nausea and vomiting: Medications can now control these symptoms so that many men experience little or no nausea.

Immunotherapy

Biological therapy, also called immunotherapy, uses your body's immune system to fight cancer cells. One type, called Provenge (sipuleucel-T), has been developed to treat advanced, recurrent prostate cancer.11

Provenge is a therapeutic cancer vaccine that is approved for men with prostate cancer that have developed resistance to hormone therapies and have either no symptoms or only mild symptoms of the disease. Like vaccines that stimulate the body to fight off bacteria or viruses, Provenge stimulates a man's body to fight off cancer cells.

Provenge consists of autologous (coming from the patient himself) peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated during a defined culture period with a specific stimulating product.

Provenge is thought to work through APCs to stimulate T-cell immune response targeted against prostatic acid phosphatase (PAP), an antigen that is highly expressed in most prostate cancer cells, as this treatment can induce the recruitment of CD4 and CD8 T cells to the tumor microenvironment.12

With this therapy, a man's blood is first withdrawn (in a procedure called plasmapheresis that is similar to dialysis) and his T regulatory cells are isolated. The Tregs are then exposed to prostatic acid phosphatase, a molecule found on the surface of prostate cells, training the Tregs to recognize these cancer cells as invaders. The cells are injected back into the man to do their job.

Monitoring progress can be challenging for men with Provenge, as PSA levels and the size and extent of tumors does not change. Yet, this can extend survival by several months with minimal side effects.11 It has more benefit when the medication is started sooner, as the effect is cumulative over time.

Combining radiation therapy with immunotherapy appears to make the treatment work better via a process called the abscopal effect. The dying cells from radiation help the immune cells identify tumor-specific molecules so they can hunt them down in other areas of the body.

Clinical Trials

There are a number of different clinical trials in progress looking for newer and better ways to treat prostate cancer (or ways that have fewer side effects).13 Drugs that are being studied include other immunotherapy drugs as well as targeted therapies, treatments that target specific genetic abnormalities in cancer cells or the growth pathway of cancer cells. PARP inhibitors are medications that have been evaluated for people with breast cancer and may be helpful for men with prostate cancer who have BRCA gene mutations.

Treatment of Metastases

Prostate cancer can spread to bones and other regions of the body. General treatments for prostate cancer can also address metastases, but specific treatments are also used at times.

Bone metastases can be treated in a number of different ways. Treatment can reduce pain and also reduce the risk of complications of bone metastases such as fractures and spinal cord compression.

Treatment options for bone metastases include:

Radiation therapy

Radiopharmaceuticals: Metastron (strontium-89), Quadramet (samarium-153), and radium-223 can be injected and delivers radiation directly to bones. These treatments are particularly helpful if bone metastases are widespread or present in different areas of the body.

Bone-modifying drugs: Bone-modifying drugs work by changing the microenvironment of bones and can be used to both treat and prevent bone metastases. Agents include the bisphosphonate drug Zometa (zoledronic acid) and Xgeva or Prolia (denosumab).

Liver metastases may also sometimes be treated specifically. Liver metastases can be very serious with prostate cancer and are most often treated with general treatments for metastatic cancer. For some men, however, SIR

-Spheres to treat liver metastases may be an option when other treatments are not controlling the disease in the liver.

Complementary Treatments

At present, there are no alternative treatments that can cure prostate cancer or extend life, but studies looking at issues ranging from diet to medications not traditionally used for prostate cancer indicate that such options may play a complementary role in the future.

Diet

A healthy, balanced diet is necessary for healing from the treatments used for prostate cancer.

A 2016 study suggested that foods high in lycopene, such as tomato sauces, may have some benefit for men with high-risk prostate cancer.

There has been some thought that a diet high in meat and animal fat may be detrimental, but this is not well understood at this time.

Vitamins

There is some evidence that vitamins, such as taking a multivitamin, zinc, or calcium, may increase the mortality from prostate cancer. While it's too soon to know the significance of vitamins with prostate cancer, some vitamin and mineral supplements may interfere with treatment. It's important to talk to your healthcare provider not only about your prescription medications, but any over-the-counter medications, vitamins, or dietary supplements you wish to take.

Metformin

It appears that men who have diabetes and prostate cancer live longer when treated with metformin than with other diabetes medications, but the drug is also being studied for its possible role in treating some cancers themselves. Its role in the treatment of prostate cancer is still uncertain, however.

Statins

Statins are the category of cholesterol-lowering drugs, such as Lipitor (atorvastatin), that many people are familiar with. In studies to date, it appears that men treated with statins have a reduced risk of death and a higher cure rate from prostate cancer.

Aspirin

Studies have looked at the role that aspirin may have in the survival from many cancers.

A large 2014 study published in the *Journal of Clinical Oncology* found that low-dose aspirin was associated with a lower risk of dying from prostate cancer, but only for those who had high-risk tumors.

The benefits of treatment need to be weighed against the possible risks (such as bleeding ulcers), and it's important to talk to your healthcare provider if you are considering using aspirin.

Foregoing Treatment

There are people who may choose to forego treatment, even if they are a candidate for it. For some men, a short life expectancy or other serious medical problems may result in this choice. In this case, a man may feel that the risks or side effects of treatments outweigh their potential benefits.

Since what will happen if prostate cancer goes untreated will vary depending on many factors, it's important to clearly ask your practitioner about your case. Understanding the possible course of your cancer and how likely progression is to occur can help you make an educated decision about your care. Choosing to forego treatment is certainly reasonable in the right circumstances but requires a careful and thoughtful discussion with your healthcare provider and family.

Making Decisions

There are a number of different doctors that treat prostate cancer, including urologists, radiation oncologists, medical oncologists, and primary care physicians such as internists and family physicians. You may get differing opinions as to the best treatment for you depending on a practitioner's clinical focus.

By learning about your disease and consulting more than one physician, you can weigh the different options for yourself and become an active voice in your care.

Many people find it helpful to get a second opinion at one of the National Cancer Institute-designated cancer centers.14 These centers are not only known for their top-notch specialists in the field of cancer but often offer more clinical trials than community hospitals. Some specialists may design a plan of treatment that can then be undertaken by your community physician.

Frequently Asked Questions

Why would healthcare providers recommend not treating prostate cancer?

Prostate cancer grows very slowly. In the early stages, it may cause no problems, while surgery or other treatments *may* cause problems and side effects.2 Depending on your overall health and the stage of your cancer, it might be better to leave it alone for the time being. If the cancer advances, your healthcare provider may recommend actively treating the cancer.

When is surgery recommended for prostate cancer?

By stage 2, prostate cancer may require surgery.15 Treatment at this point can help ensure the cancer doesn't spread beyond the prostate and cause symptoms. Signs of stage 2 include a PSA test reading between 10 and 20 and a Gleason score of 6 or less.

Is stage 4 prostate cancer curable?

No, but it is treatable. Although the tumors may have spread to lymph nodes or distant organs, stage 4 cancer can be managed by treatments such as surgery, hormone therapy, chemotherapy, radiation, or a combination of therapies.15

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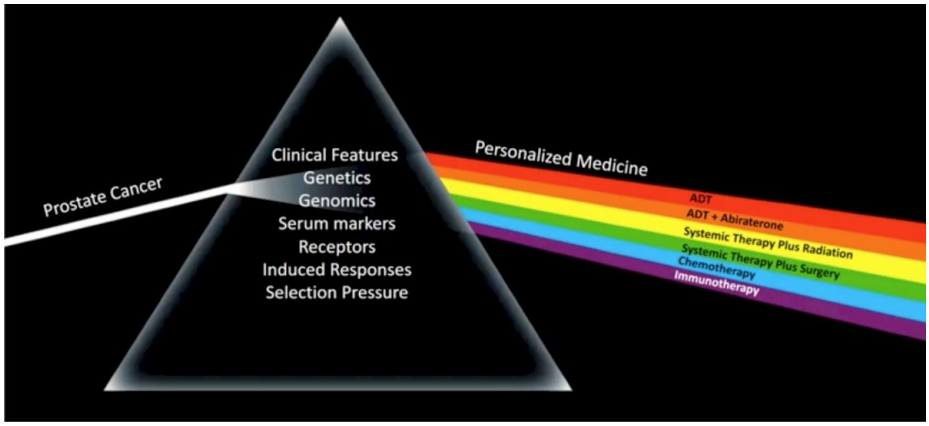
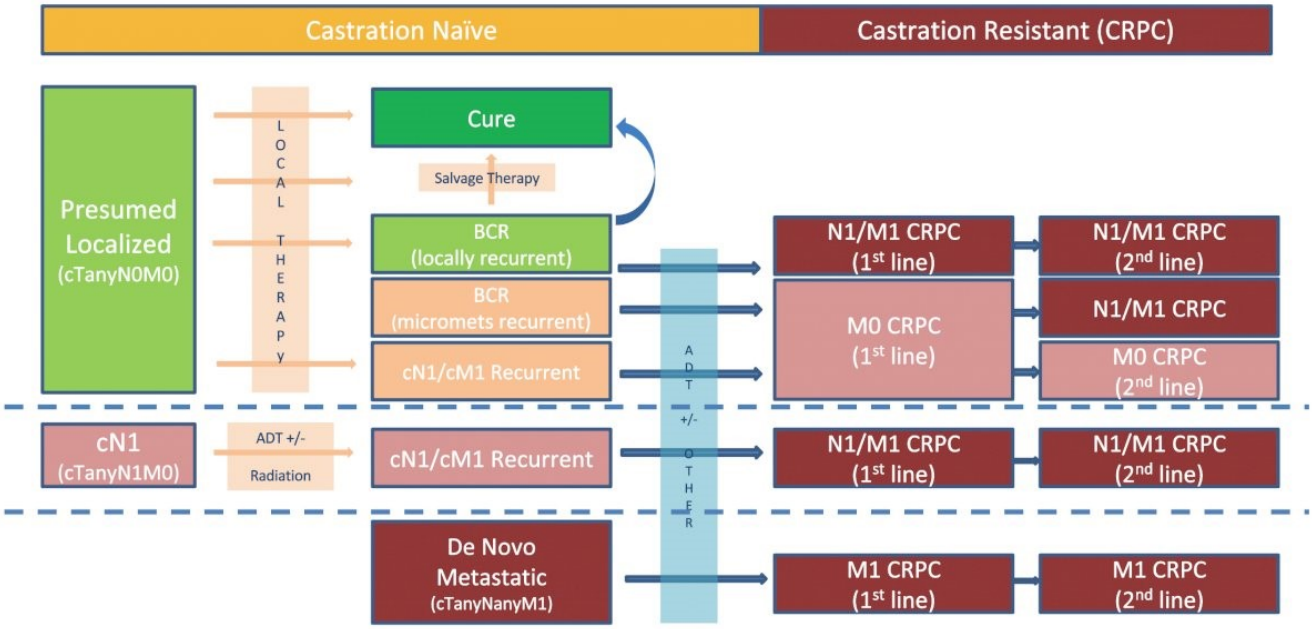
AUA 2021: State-of-the-art Lecture: Personalized Medicine in the Management of Prostate Cancer Across the Patient Care Continuum

(UroToday.com) The American Urologic Association annual meeting included a State-of-the-Art Lecture by Dr. Brian Chapin who discussed personalized medicine in the management of prostate cancer across the patient care continuum. Dr. Chapin notes that the way we think about the personalized approach to prostate cancer therapy involves seeing a patient in the clinic and assessing them on a number of factors (clinical features, genetics, genomics, serum markers, receptors, induced responses, and selection pressures) and then developing a personalized approach to their treatment plan:

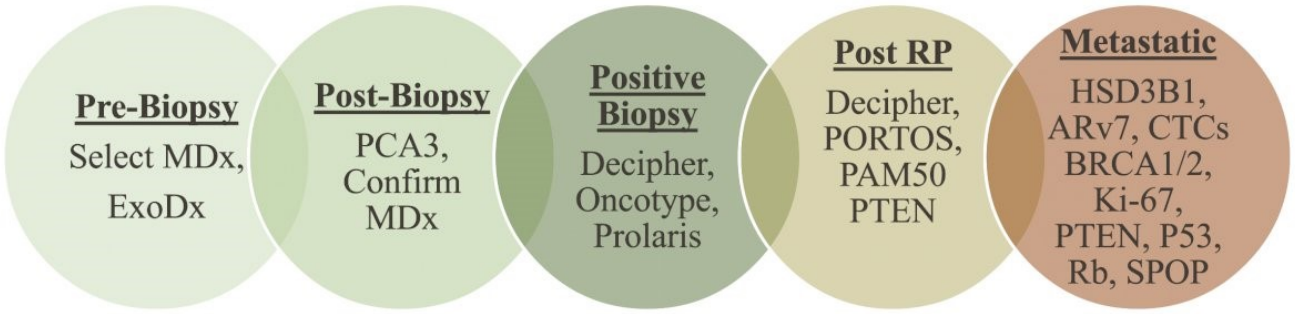


In setting the stage for personalized care, it is important to understand the available treatment options in the castration-naïve setting, as well as the castration resistant setting:



Dr. Chapin notes that personalized care is compartmentalization by stage, histology and biology. Traditionally we have delineated care by stage of disease in combination with histologic considerations (ie. neuroendocrine, ductal, adenocarcinoma). More recently, there has become an increasingly more sophisticated approach, with regards to assessing the androgen receptor axis (TMPRSS2-ERG, SPOP, AR responsive), loss of tumor suppression (p53, PTEN, Rb), DDR mutations (BRCA, CDK12, FANCONI, CHEK1/2), and mismatch repair (MSI, Lynch syndrome).

Compartmentalization allows for better risk stratification, for example balancing arms in a clinical trial by using stratification factors (ie. M1a/b versus M1c) and balancing groups in retrospective studies by utilizing matching or propensity scoring (ie. NCDB, SEER database). However, this can also generate selection bias in retrospective cohort series, for example in patients with occult node positive prostate cancer, some patients will undergo a completion prostatectomy whereas others will have their radical prostatectomy aborted (thus, unable to compare outcomes). Many of us think of personalized care in prostate cancer by way of DNA, RNA, proteins and receptors, such as in the pre-biopsy, post-biopsy, positive biopsy, post-radical prostatectomy, and metastatic settings:



Dr. Chapin emphasizes that it is critically important to delineate between prognostic versus predictive biomarkers. Prognostic biomarkers are a variable associated with favorable or unfavorable outcomes for patients in the absence of treatment. Predictive biomarkers are a variable used to identify patients or groups of patients most likely to benefit from a specific therapy, for example a patient with a DNA damage repair mutation being a candidate for PARP inhibitor treatment, or a patient with a mismatch repair deficiency being a candidate for anti-PD1 antibody treatment. Prognostic variables can be used incorrectly thus mistakenly influencing management. For example, genomic tests on prostate biopsies have all been based on treated prostate cancer patients, thus these findings may not be applicable to an active surveillance cohort. Findings from these genetic tests are used to make changes in management decisions, resulting in Medicare approval. Dr. Chapin states that it is important to remember that no randomized trials have reported outcomes (although there are several ongoing) assessing if genomic tests improve patient outcomes, and in fact reflexive genomic testing may be detrimental to patients.

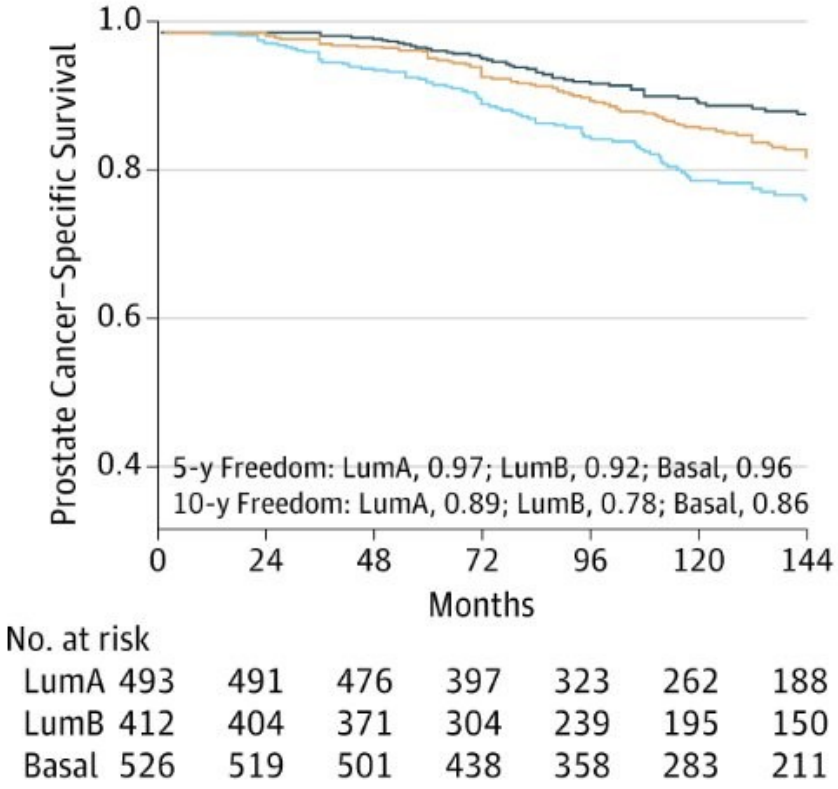
Dr. Chapin then discussed several potential predictive markers and prospective trials. The PAM50 gene expression classifier was previously described in the breast cancer literature, but has since been applied to prostatectomy specimens. Zhao et al.[1] applied the classifier to 3,782 samples (1,567 retrospective, 2,215 prospective) noting that the PAM50 classifier consistently segregated prostate cancer into three subtypes in both retrospective and prospective cohorts:

Luminal A (retrospective 34.3%; prospective 33.3%)

Luminal B (retrospective 28.5%; prospective 32.6%)

Basal (retrospective 37.1%; prospective 34.1%)

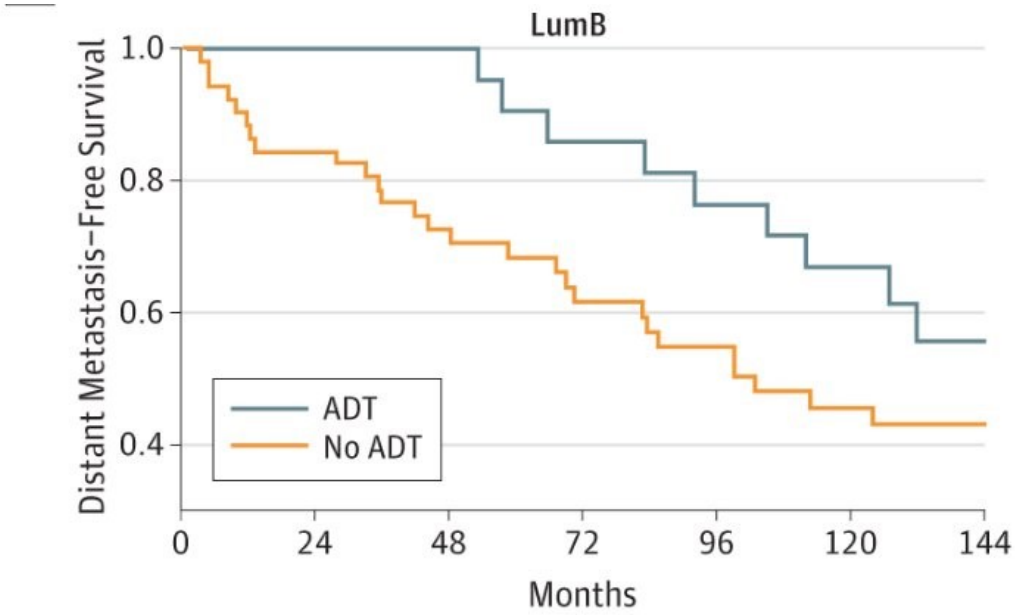
Luminal A, luminal B, and basal curves separate based on PAM50 gene expression, with basal tumors having worse prostate-cancer specific survival:



No. at risk

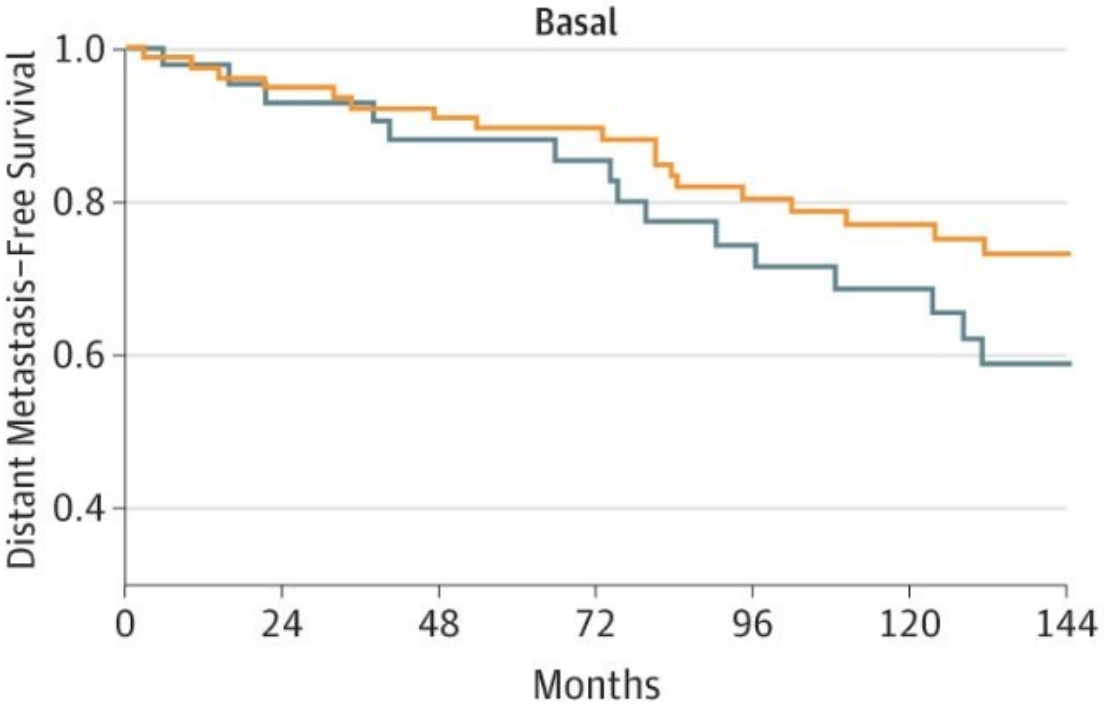
LumA	493	491	476	397	323	262	188
LumB	412	404	371	304	239	195	150
Basal	526	519	501	438	358	283	211

When assessing luminal B and basal tumors with regards to response to ADT, this study suggests there may be a benefit to treatment of luminal B patients with ADT but no benefit seen in those with basal tumors:



No. at risk

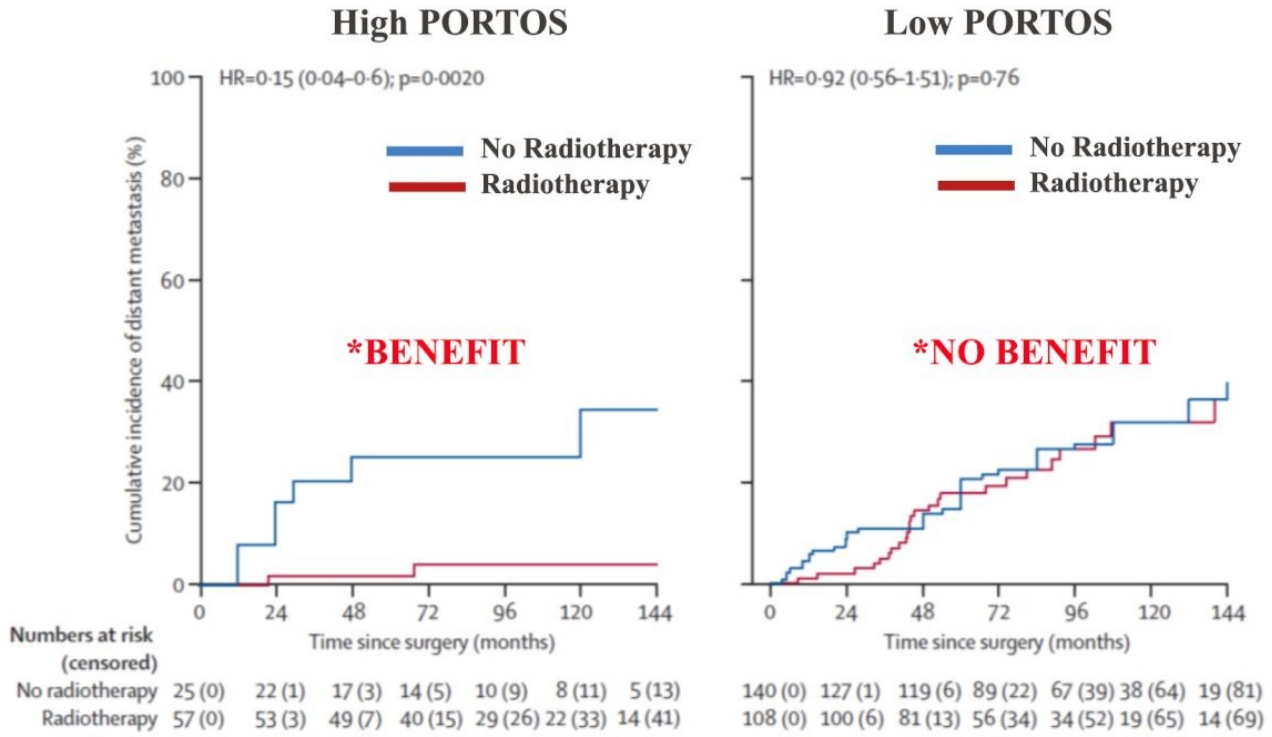
ADT	21	21	21	18	16	14	9
No ADT	52	43	35	27	24	18	14



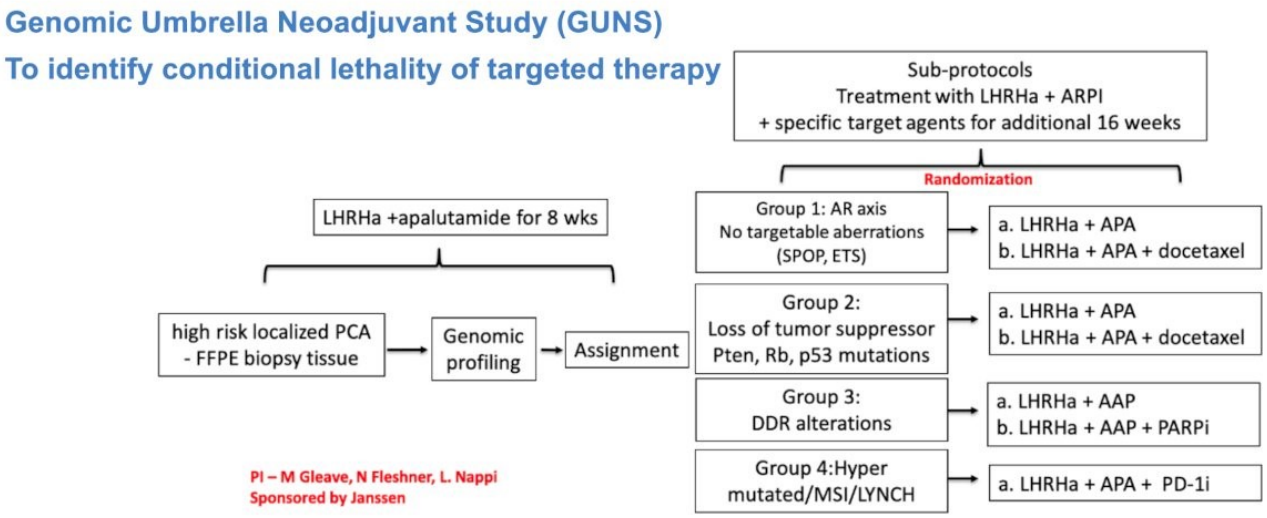
No. at risk

ADT	42	39	37	32	26	22	18
No ADT	76	72	68	61	52	43	30

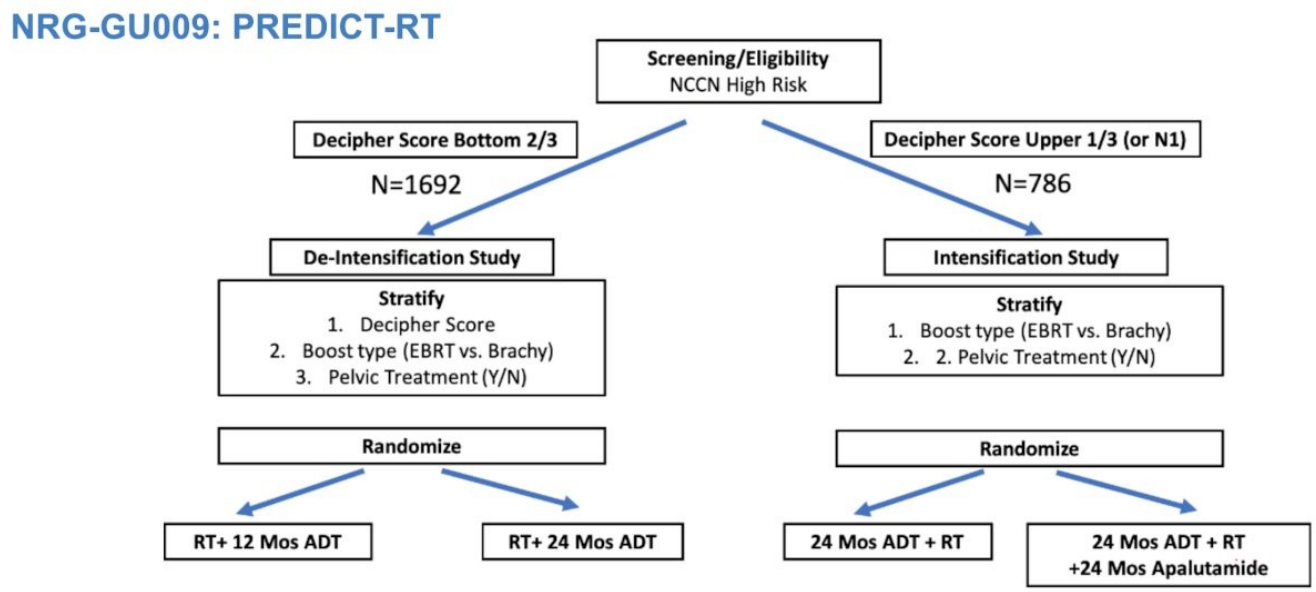
Another example is the post-operative radiation therapy outcomes score (PORTOS), which is a genetic prediction score for post-op radiation. PORTOS is made up of 24 genes selected from a training set of 196 men and validate in a separate cohort of 330 men, with a clinical endpoint of metastasis over 10 years of follow-up.[2] In this study, patients with a high PORTOS score had a benefit in cumulative incidence of distance metastasis with radiotherapy (HR 0.15, 95% CI 0.04-0.60), whereas patients with a low PORTOS score (HR 0.92, 95% CI 0.56-1.51) did not have a benefit with radiotherapy:



Biomarker examples have also been described in the advanced prostate cancer setting, specifically assessing androgen indifferent or aggressive variant prostate cancer. In a phase 1-2 trial assessing cabazitaxel plus carboplatin for men with mCRPC, at a median follow-up of 31.0 months, combination cabazitaxel plus carboplatin improved the median progression-free survival from 4.5 months (95% CI 3.5-5.7) to 7.3 months (95% CI 5.5-8.2; HR 0.69, 95% CI 0.50-0.95) with cabazitaxel alone.[3] Dr. Chapin notes that what is particularly interesting is that for patients with a positive aggressive variant prostate cancer molecular signature, there was an improvement in overall survival with the addition of platinum based chemotherapy, whereas there was no benefit in those that were aggressive variant prostate cancer molecular signature negative. Dr. Chapin highlighted that there are several trials ongoing in the localized setting assessing a personalized approach, including the Genomic Umbrella Neoadjuvant Study (GUNS):



Decipher is a 22 gene classifier that provides risk stratification based on radical prostatectomy specimen analysis, which is prognostic for metastasis. However, there is no data on predictive ability, which is undergoing prospective evaluation in the NRG-GU009 PREDICT-RT trial:



Importantly, there are several barriers to overcome in the era of personalized medicine, including (i) assessing if findings are transferrable across stages of the disease; (ii) tumor heterogeneity, whether intertumoral, intratumoral, or comparing a metastases to the primary tumor; (iii) in order to move from prognostic to predictive markers, prospective trials are required; (iv) it is important to determine drivers in the setting of co-occurences (ie. DDR, +/- p53, +/- Rb1, +/- PTEN); and (v) assess selection pressures over time (ie. the predominant clone).

Dr. Chapin concluded his presentation with the following take-home messages from his presentation of personalizing medicine in the management of prostate cancer:

Progress is being made in the personalized care of prostate cancer patients

It is important to delineate between predictive versus prognostic markers

We need validation of markers to predict a therapeutic benefit

Prospective trials with generation of biobanks are needed moving forward

Skeptical optimism is appropriate until validation is completed

Presented by: Brian Chapin, MD, Associate Professor of Urology, MD Anderson Cancer Center, Houston, TX

Written by: Zachary Klaassen, MD, MSc – Urologic Oncologist, Assistant Professor of Urology, Georgia Cancer Center, Augusta University/Medical College of Georgia, @zklaassen_md on Twitter during the 2021 American Urological Association, (AUA) Annual Meeting, Fri, Sep 10, 2021 – Mon, Sep 13, 2021.

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Certain Types of Cancer May Increase the Risk of Developing Guillain-Barré

MINNEAPOLIS - People who have certain types of cancers may have an increased risk of having new onset Guillain-Barré syndrome, according to a study published in the March 2, 2022, online issue of *Neurology*®, the medical journal of the American Academy of Neurology. Researchers found an increased risk in people who had lymphomas and blood cancers, as well as in those who had lung, prostate or breast cancers. The study does not prove that cancer causes Guillain-Barré syndrome. It only shows an association.

Guillain-Barré syndrome is a rare neurologic disorder in which the immune system attacks nerve cells. Symptoms typically start with weakness and tingling in the feet and legs, which spread to the upper body and arms and may progress to paralysis. Although it can be life-threatening, most people recover with few remaining problems. An exact cause of Guillain-Barré syndrome is unknown, but it can occur after gastrointestinal or respiratory infections.

For the study, researchers reviewed Danish national registries. Over a 30-year period, they identified 2,414 people who were diagnosed with Guillain-Barré syndrome. For each person diagnosed with the disease, researchers also identified 10 people without the disease who were matched for age and sex at the time of Guillain-Barré diagnosis, for a total of about 24,000 people who did not have Guillain-Barré.

"While a majority of Guillain-Barré syndrome cases develop after an infection, there are still many cases that do not," said study author Lotte Sahin Levison, MD, PhD, of Aarhus University Hospital in Denmark. "Previous studies have suggested there may be a link between cancer and Guillain-Barré syndrome, but just how often people develop Guillain-Barré after a cancer diagnosis has not been well-studied. Our research looked at the population of nearly six million people in Denmark and found that people diagnosed with cancer may have a higher risk of developing Guillain-Barré."

Researchers then identified people in the study who had a recent cancer diagnosis. This was defined as a cancer diagnosis up to six months before or two months after a Guillain-Barré diagnosis. Recent cancer diagnosis was

determined for people with Guillain-Barré and for the people matched to them without the disease. Of the people who had Guillain-Barré, 49 people, or 2%, had a recent cancer diagnosis.

Of the people who did not have Guillain-Barré, 138 people, or 0.6%, had a recent cancer diagnosis. Researchers found that people recently diagnosed with cancer had over a three-and-a-half times greater risk of developing Guillain-Barré than people without cancer. After adjusting for surgery, infections and other health problems in a subset of participants, researchers still found a nearly a three times greater risk.

When looking at specific cancers, people with cancers like lymphomas had a seven times greater risk, people with lung or *prostate cancer had a five-and-a half times greater risk*, and those with breast cancer had a five times greater risk. "While our study suggests that people with cancer have a greater risk of developing Guillain-Barré syndrome, it is important that people with cancer know the overall risk of developing Guillain-Barré is still very small," said Levison. "More research is now needed. Our results suggest that yet unidentified factors present in several types of cancer may contribute to this increased risk."

A limitation of the study was that people with Guillain-Barré may have been more closely screened for cancer compared to people who did not have Guillain-Barré, so some cancer cases in the second group may have been missed.

The study was supported by the Bevica Foundation, teacher Svend Aage Nielsen Wacherhausens Foundation, the Aase and Ejnar Danielsen Foundation and the A.P. Moller Foundation.

Learn more about Guillain-Barré syndrome at BrainandLife.org, home of the American Academy of Neurology's free patient and caregiver magazine focused on the intersection of neurologic disease and brain health. Follow *Brain & Life*® on Facebook, Twitter and Instagram. When posting to social media channels about this research, we encourage you to use the hashtags #Neurology and #AANscience.

The American Academy of Neurology is the world's largest association of neurologists and neuroscience professionals, with 38,000 members. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a doctor with specialized training in diagnosing, treating and managing disorders of the brain and nervous system such as Alzheimer's disease, stroke, migraine, multiple sclerosis, concussion, Parkinson's disease and epilepsy.

For more information about the American Academy of Neurology, visit AAN.com or find us on Facebook, Twitter, LinkedIn, Instagram and YouTube.

sciencedaily.com

Metastatic prostate cancer on the rise since decrease in cancer screenings

A new study from Keck Medicine of USC finds that the incidence rate of metastatic prostate cancer has significantly increased for men 45 and older and coincides with recommendations against routine prostate cancer screenings.

"This study is the first to document a continued rise in metastatic prostate cancer using the most up-to-date population dataset," said Mihir M. Desai, MD, MPH, a urologist with Keck Medicine and co-lead author of the study. "The discovery has important ramifications for men because prostate cancer, when caught early, typically through a screening, is very treatable and often curable."

Desai is also a professor of clinical urology at the Keck School of Medicine of USC and an associate member of the USC Norris Comprehensive Cancer Center, part of Keck Medicine.

Routine prostate-specific antigen (PSA) screenings for prostate cancer began in the United States almost three decades ago. PSA screenings measure the amount of PSA in the blood, and elevated levels can indicate cancer.

The introduction of screenings resulted in drops in both metastatic prostate cancer and prostate cancer deaths. However, the benefit of routine screenings was counterbalanced by risks of overdiagnosis and overtreatment of low-risk prostate cancer.

In 2008, the United States Preventive Services Task Force (USPSTF), a leading national organization in disease prevention and evidence-based medicine, recommended against routine PSA screening for men older than 75. This was followed by a recommendation against screening for all men in 2012.

Research shows that prostate cancer screenings for men declined after the recommendations changed across all age groups and racial backgrounds.

Keck Medicine researchers wanted to assess metastatic prostate cancer trends before and after the USPSTF recommendations against screenings.

They identified men 45 and older with a diagnosis of invasive prostate cancer from 2004-2018 through the Surveillance, Epidemiology and End Results (SEER) Program cancer incidence database.

From 2004-2018, the last year for which data was available, more than 836,000 prostate cancer patients 45 or older were recorded in the SEER database. Of these, 26,642 cases of metastatic prostate cancer were reported in men 45-74, and 20,507 cases in men 75 or older.

Among the 45-74 age group, the incidence rate of metastatic prostate cancer remained stable during 2004-2010, then increased 41% during 2010-2018. For men 75 and older, the incidence rate decreased in 2004-2011, then increased 43% from 2011-2018. For both age groups, the increases were across all races.

The researchers note that these increases stand in contrast to the decreasing trends in incidence of metastatic prostate cancer between 2004-2009, before the USPSTF stopped recommending routine PSA screenings for men.

The authors also discuss the possibility that other factors besides the change in screening recommendations in 2008 and 2012 could play a role in the uptick in cancer cases, such as the use of new, cutting-edge diagnostic and staging tools that are better able to detect low-volume (less invasive) metastatic prostate cancer.

However, they conclude that such techniques are not widespread, and typically not used for first-time cancer detection, so are unlikely to be of significance in the findings.

"This data is very important as it indicates the need to constantly reassess the impact of policy decisions," said Giovanni Cacciamani, MD, MSc, co-lead author of the study, an assistant professor of research urology and radiology at the Keck School and an associate member of USC Norris. "Otherwise, we may see a continued rise in metastatic prostate cancer."

The original concerns for stopping the screenings -- that they led to overdiagnosis and overtreatment of low-risk prostate cancer -- may also be outdated, say the authors.

"Urologic centers of excellence, including USC Urology, are continually researching ways to leverage technologies to optimize patient outcomes and decrease side effects of treatment," said Inderbir Gill, MD, chairman of the Catherine and Joseph Aresty Department of Urology, distinguished professor of urology at the Keck School, executive director of the USC Institute of Urology and a member of USC Norris. "More refined strategies, including biomarkers and magnetic resonance imaging, have already increased detection of clinically significant cancers, while active surveillance is increasingly used for low-risk and favorable intermediate-risk disease, thus mitigating the risks of overtreatment."

Other Keck Medicine study authors include Juanjuan Zhang, a statistician at the Keck School; Lihua Liu, PhD, associate professor of clinical population and public health sciences at the Keck School, director and principle investigator of the SEER Program and a member of USC Norris; and Andre Abreu, MD, a urologist with Keck Medicine who directs the Center for Targeted Biopsies & Focal Therapy at the USC Institute of Urology.

177Lu-PSMA radioligand therapy effectiveness in metastatic castration-resistant prostate cancer: An updated systematic review

and meta-analysis

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Abstract

Background

An updated systematic review and meta-analysis of relevant studies to evaluate the effectiveness of prostate-specific membrane antigen (PSMA)-targeted endoradiotherapy/radioligand therapy (PRLT) in castration resistant prostate cancer (CRPC).

Methods

A systematic search was performed in July 2020 using PubMed/Medline database to update our prior systematic review. The search was limited to papers published from 2019 to June 2020. A total of 472 papers were reviewed. The studied parameters included pooled proportion of patients showing any or ≥50% prostate-specific antigen (PSA) decline after PRLT. Survival effects of PRLT were assessed based on pooled hazard ratios (HRs) of the overall survival (OS) according to any PSA as well as ≥50% PSA decline after PRLT. Response to therapy based on ≥50% PSA decrease after PRLT versus controls was evaluated using Mantel-Haenszel random effect meta-analysis. All p values < 0.05 were considered as statistically significant.

Results

A total of 45 publications were added to the prior 24 studies. 69 papers with total of 4157 patients were included for meta-analysis. Meta-analysis of the two recent randomized controlled trials showed that patients treated with ^{177}Lu-PSMA 617 had a significantly higher response to therapy compared to controls based on ≥50% PSA decrease. Meta-analysis of the HRs of OS according to any PSA decline and ≥50% PSA decline showed survival prolongation after PRLT.

Conclusions

PRLT results in higher proportion of patients responding to therapy based on ≥50% PSA decline compared to controls. Any PSA decline and ≥50% PSA decline showed survival prolongation after PRLT.

Advances in knowledge: This is the first meta-analysis to aggregate the recent randomized controlled trials of PRLT which shows CRPC patients had a higher response to therapy after PRLT compared to controls

Clinical and pathological features associated with circulating tumor DNA content in real-world patients with metastatic prostate cancer

Emmanuel S. Antonarakis MD, Marni Tierno PhD, RN, Virginia Fisher PhD, Hanna Tukachinsky PhD, Sonja Alexander MS, RN, Omar Hamdani PhD, Matthew C. Hiemenz MD … See all authors

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Abstract

Background

Liquid biopsy is a powerful tool that can enable treatment decisions for metastatic prostate cancer patients with difficult-to-biopsy tumors. However, the detection of genomic alterations via liquid biopsy is limited by the fraction (tumor fraction [TF]) of circulating tumor DNA (ctDNA) within the total cell-free DNA content. While prior work has preliminarily correlated TF with clinical features of prostate cancer, we sought to validate and provide additional resolution, such that a clinical practitioner might anticipate the probability of successful liquid biopsy profiling leveraging commonly assessed clinical and laboratory features.

Methods

A total of 813 liquid biopsy specimens were assessable, with 545 associated with a PSA prostate specific antigen measurement, collected in standard-of-care settings across approximately 280 US academic or community-based cancer clinics from September 2018 to July 2021. Deidentified data were captured into a real-world clinicogenomic database (CGDB). Comprehensive genomic profiling (CGP) was performed on extracted cell-free DNA from liquid biopsy samples.

Results

In multivariable models, higher PSA level, lower hemoglobin, lower albumin, higher alkaline phosphatase (all $p < 0.001$), and collection of liquid biopsy blood draw within 60 days of new treatment initiation ($p = 0.002$) were the most strongly associated features with higher TF. At PSA levels of <5 ng/ml, 43% of patients had a TF of <1% indicating an increased likelihood of unevaluable results. Conversely, at PSA levels of >5 ng/ml, 78% of patients had a TF of at least 1% and 46% had a TF of ≥10%, suggesting improved sensitivity for detection of targetable alterations.

Conclusions

Universal genomic profiling of prostate cancers will require complementary use of liquid biopsy and tumor tissue profiling for suitable patients. The likelihood of adequate ctDNA shedding into plasma is one consideration when deciding whether to pursue CGP via liquid biopsy versus tumor profiling. Our real-world data suggest that PSA < 5 ng/ml is associated with lower ctDNA yield on liquid biopsy, potentially increasing the incidence of negative results or a need for confirmation with tissue testing.

Prostate Cancer Patients to Reap the Benefits of "Seeds" Planted by NRG Oncology/RTOG 0526

Niluja Thiruthaneeswaran, MBBS, PhD

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There is an increasing trend to offer salvage treatments for prostate cancer patients with local recurrence after definitive radiation therapy. This swing in the pendulum is in unison with improvements in local imaging modalities to detect recurrence or persistence of disease. Salvage options include radical prostatectomy, cryotherapy, high-intensity focused ultrasound (HIFU), brachytherapy, and more recently stereotactic body radiation therapy (SBRT). There is no clear superiority of any of these methods, nor is there consensus on patient selection criteria. Although salvage treatments after definitive prostate radiation therapy have the potential to be curative, their uptake in practice has been associated with a high level of caution, mainly owing to concerns regarding late toxicity as well as skepticism about long-term efficacy. More than 150, largely retrospective, studies have been published in this setting, of which just under 40 have used brachytherapy as the salvage modality. 1

,2

The heterogenous patient cohort, the multifocal nature of disease recurrence, the complex radiobiology, and potential limitations in technical expertise all pose challenges to conducting a robust clinical trial in this population. Crook et al are to be commended on executing the first multicenter phase 2 study of salvage low-dose-rate (LDR)

brachytherapy for local recurrence of prostate cancer previously treated with external beam radiation therapy (EBRT). 3

marketwatch.com

Merck to stop clinical trial testing Keytruda with AstraZeneca's Lynparza in prostate cancer patients

Jaimy Lee

Merck & Co. Inc. MRK, -0.85% said Tuesday that it will stop a clinical trial evaluating Keytruda with AstraZeneca's AZN, 0.67% AZN, +0.35% Lynparza in advanced prostate cancer patients because the combination therapy doesn't work. The company said the drugs did not show an improvement in overall survival, which is one of the trial's primary endpoints. The companies will continue to test the Keytruda-Lynparza combination in patients with other types of cancers.

The Food and Drug Administration last week approved Lynparza as a treatment for some people with early-stage breast cancer; it was initially approved to treat ovarian cancer. Keytruda has been approved to treat several types of cancer and is Merck's top-selling drug, bringing in $17.2 billion in sales in 2021. Merck's stock is up 1.5% so far this year, while the broader S&P 500 SPX, +1.16% has declined 12.4%.

Evaluation of selective bone scan staging in prostate cancer – external validation of current strategies and decision-curve analysis

Mrunal D. Hiwase, Alex Jay, Norma Bulamu, Johnathan Teh, Felix Paterson, Ganessan Kichenadasse, Andrew D. Vincent, Michael O'Callaghan & South Australian Prostate Cancer Clinical Outcomes Collaborative (SA-PCCOC)

Prostate Cancer and Prostatic Diseases (2022)Cite this article

Abstract

Background

Recommendations for staging newly diagnosed prostate cancer patients vary between guidelines and literature.

Methods

Our objective was to validate and compare prediction models selecting newly diagnosed prostate cancer patients for bone scan staging. To achieve this, we validated eleven models in a population-based cohort of 10,721 patients diagnosed with prostate cancer between 2005 and 2019. The primary outcome was net-benefit. This was assessed at different balances of conservatism and tolerance, represented by preference ratio and number-willing-to-test (NWT). Secondary outcomes included calibration slope, calibration-in-the-large (intercept), and discrimination measured by Area-under-the-receiver-operator-characteristics curve (AUC).

Results

For preference ratios less than 1:39 (NWT greater than 40), scanning everyone provided greater net-benefit than selective staging. For preference ratios 1:39 to 3:97 (NWT 33–40), the European Association of Urology (EAU) 2020 guideline recommendation was the best approach. For preference ratios 3:97–7:93 (NWT 14–33), scanning EAU high-risk patients only was preferable. For preference ratios 7:93–1:9 (NWT 10–13), scanning only Gnanapragasam Group 5 patients was best. All models had similar fair discrimination (AUCs 0.68–0.80), but most had poor calibration.

Conclusions

We identified three selective staging strategies that outperformed all other approaches but did so over different ranges of conservatism and tolerance. Scanning only EAU high-risk patients provided the greatest net-benefit

over the greatest range of preference ratios and scenarios, but other options may be preferable depending upon the local healthcare system's degree of conservatism and tolerance.

medscape.com

As Predicted: Jump in Metastatic Prostate Cancer Diagnoses

M. Alexander Otto, MMS, PA

The incidence of metastatic prostate cancer shot up in the United States after the US Preventive Services Task Force recommended against routinely screening men with the prostate-specific antigen (PSA), shows a report published online today in *JAMA Network Open*.

It was a consequence that many experts in prostate cancer predicted at the time the recommendation was made — initially in 2008 against routine screening in men older than 75 years, and then in all men in 2012.

The thinking was that the harms of screening all men — leading to unnecessary prostatectomies and other treatments in many men — outweighed the benefits of catching early high-risk disease in fewer men. Screening rates plummeted as a result.

But experts in prostate cancer warned that the move, while reducing overdiagnosis and overtreatment, would have the unfortunate consequence of underdiagnosis and, consequently, nondetection of the cases of prostate cancer that would spread.

The new findings are the latest to suggest that this is, in fact, what happened, and echo similar findings previously reported by *Medscape Medical News*.

For this study, investigators at the University of Southern California, Los Angeles, analyzed the incidence of metastatic prostate cancer (mPCa) in the Surveillance, Epidemiology, and End Results (SEER) database from 2004-2018, with 2018 being the latest data available.

SEER captures about 28% of the US population and recorded almost 50,000 new mPCa cases over the period.

Among men 45-75 years old, the incidence of mPCa increased 41% from when USPSTF recommended against screening through 2018, which translated to an annual percentage change (APC) of 5.3%.

Among men 75 years and older, mPCa rates jumped 43% through 2018, an APC of 6.5%.

The researchers did not find an increase in deaths from prostate cancer, but given the 5-7 years median survival, it might be too early to tell.

"The observation of a rising incidence of mPCa in itself does not imply that screening practices should be changed. The overall risk vs benefit of PSA-based screening is extremely complex and must take into account various other factors that impact the overall health of the community," say investigators, led by Mihir Desai, MD, a clinical urology professor at USC.

However, screening practices have already changed. The USPSTF withdrew its objections to screening in 2018, and instead recommended personalized decision-making for men 55-69 years old, citing new evidence that screening prevents metastatic disease and reduces PCa mortality more than previously recognized, Richard Hoffman, MD, MPH, an internal medicine professor at the University of Iowa, Iowa City, said in an accompanying editorial.

The study's trends in mPCa "might be transitory because the screening guidelines have" changed, Hoffman writes.

For now, clinicians should "consistently address screening with men who are healthy enough to benefit" from catching dangerous tumors early and engage them "in shared decision-making discussions to" strike the right balance between minimizing overdiagnosis and catching high-risk tumors before they spread, he said.

Easier said than done, but the field is advancing. Active surveillance, instead of surgery, for what seem to be low-risk tumors is one step in the right direction, Hoffman commented.

No external funding was reported. Desai is a consultant for Procept Biorobotics and Auris Surgical. Hoffman reported royalties from UpToDate and fees from law firms as an expert witness on prostate cancer screening cases.

JAMA Netw Open. Published online March 14, 2022. Full text, Editorial

M. Alexander Otto is a physician assistant with a master's degree in medical science and a journalism degree from Newhouse. He is an award-winning medical journalist who worked for several major news outlets before joining Medscape and is also an MIT Knight Science Journalism fellow. Email: aotto@mdedge.com

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Assessment after focal therapy what is the latest?

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Author Information

Current Opinion in Urology: March 11, 2022 - Volume - Issue -

doi: 10.1097/MOU.0000000000000988

Abstract

Purpose of review

To review assessment after focal therapy (FT) in the context of developments from the past two years.

Recent findings

With a paucity of high-quality studies, recent findings are primarily reliant on results from institutional-based cohorts and reports of expert consensus. Notably, oncologic treatment failure should be further stratified into recurrence in the in-field or out-of-field ablation zone, and both regions should be surveilled postoperatively. Monitoring primarily consists of periodic evaluations of prostate-specific antigen (PSA) testing and magnetic resonance imaging, with histologic sampling needed to confirm suspicion of recurrence. Recent investigations into PSA derivatives, contrast-enhanced ultrasound, and prostate-specific membrane antigen imaging have shown preliminary promise. Although postablation functional outcomes are generally accepted to be excellent, they are limited by the wide range of patient-reported measures, variability in individual practice, and low questionnaire completion rates.

Summary

There is still a need for high-level, long-term data to inform exact standardized protocols to manage patients after FT. A multifaceted approach is required to surveil patients and identify those at risk of recurrence. Embracing shared responsibility between the patient and clinician to fastidiously monitor the in-field and out-of-field ablation zones postoperatively is critical to maximize oncologic outcomes.

Implications of DNA damage repair alterations for the management of prostate cancer

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Author Information

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Abstract

Purpose of review

In this review, we summarize the prevalence of alterations in DNA damage repair (DDR) genes in prostate cancer, their clinical significance, the therapeutic strategies developed to take advantage of the impaired tumour abil-

ity to repair DNA and the diagnostic approaches available to identify patients likely to benefit from DDR-targeting agents.

Recent findings

DDR alterations are more frequent in metastatic than in localized prostate cancer and some of them associate with aggressive disease whereas the significance of others remain unclear. The most appropriate management approach for DDR-defective prostate cancer patients is unknown. Clinical trials have demonstrated the efficacy of different poly-ADP ribose polymerase inhibitors (PARPi) to treat metastatic castration-resistant prostate cancer patients with *BRCA1/2* alterations, although there may be other DDR alterations that sensitize patients to these drugs. Multiple strategies to target DDR defects are being investigated, including PARPi in combination, platinum-based chemotherapy and immunotherapy, both in earlier and late disease stages. Optimization of molecular testing is paramount for the implementation of precision oncology in prostate cancer.

Summary

Certain DDR defects present in prostate cancer have prognostic and therapeutic implications whereas the significance of other DDR alterations is yet to be elucidated.

medicalxpress.com

Early prostate cancers can harbor aggressive tumor cells

Sarah Avery

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia

Many cases of early prostate cancer are dominated by cells that are slow-growing, often leading to a clinical decision to monitor for progression before initiating treatments that can have adverse side effects.

But some of these cancers might also include a small number of aggressive cells hiding among the indolent ones like wolves in a herd of sheep. Researchers at Duke Health have identified a molecular signature that can spot these lurking threats.

Publishing online in the journal *European Urology*, the researchers said the genomic signature they have identified makes it possible to develop a test to identify which men should undergo treatment early in their diagnosis, vs. those who could safely postpone therapy, if needed at all.

"We performed single-cell RNA sequencing analysis of freshly isolated tumor cells from primary, untreated prostate cancers in men as well as advanced cancer cells," said Jiaoti Huang, M.D., Ph.D., chair of Duke's Department of Pathology and a senior author of the study.

"We discovered that a small fraction—less than 0.5%—of primary prostate cancer cells possess the genomic features of advanced and aggressive prostate cancer cells that have become resistant to hormonal therapies," Huang said. "This shows that hormonal therapy resistance can be a feature present in a small number of tumor cells early in the disease process before therapy."

Huang said the goal now is to develop a clinical assay that identifies the more dangerous cells, which could trigger earlier, aggressive treatment in some patients to avoid disease progression. Huang said Duke owns intellectual property rights on the genomic signature.

More information: Qing Cheng et al, Pre-existing Castration-resistant Prostate Cancer–like Cells in Primary Prostate Cancer Promote Resistance to Hormonal Therapy, *European Urology* (2022). DOI: 10.1016/j.eururo.2021.12.039

Citation: Early prostate cancers can harbor aggressive tumor cells (2022, January 19) retrieved 16 March 2022 from https://medicalxpress.com/news/2022-01-early-prostate-cancers-harbor-aggressive.html

Prognostic Utility of the Gleason Grading System Revisions and Histopathological Factors Beyond Gleason Grade

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Background: The International Society of Urological Pathology (ISUP) revised the Gleason system in 2005 and 2014. The impact of these changes on prostate cancer (PCa) prognostication remains unclear.
Objective: To evaluate if the ISUP 2014 Gleason score (GS) predicts PCa death better than the pre-2005 GS, and if additional histopathological information can further improve PCa death prediction.
Patients and Methods: We conducted a case–control study nested among men in the National Prostate Cancer Register of Sweden diagnosed with non-metastatic PCa 1998– 2015. We included 369 men who died from PCa (cases) and 369 men who did not (controls). Two uro-pathologists centrally re-reviewed biopsy ISUP 2014 Gleason grading, poorly formed glands, cribriform pattern, comedonecrosis, perineural invasion, intraductal, ductal and mucinous carcinoma, percentage Gleason 4, inflammation, high-grade prostatic intraepithelial neoplasia (HGPIN) and post-atrophic hyperplasia. Pre-2005 GS was back-transformed using i) information on cribriform pattern and/or poorly formed glands and ii) the diagnostic GS from the registry. Models were developed using Firth logistic regression and compared in terms of discrimination (AUC).
Results: The ISUP 2014 GS (AUC = 0.808) performed better than the pre-2005 GS when back-transformed using

only cribriform pattern (AUC = 0.785) or both cribriform and poorly formed glands (AUC = 0.792), but not when back-transformed using only poorly formed glands (AUC = 0.800). Similarly, the ISUP 2014 GS performed better than the diagnostic GS (AUC = 0.808 vs 0.781). Comedonecrosis (AUC = 0.811), HGPIN (AUC = 0.810) and number of cores with ? 50% cancer (AUC = 0.810) predicted PCa death independently of the ISUP 2014 GS.
Conclusion: The Gleason Grading revisions have improved PCa death prediction, likely due to classifying cribriform patterns, rather than poorly formed glands, as Gleason 4. Comedonecrosis, HGPIN and number of cores with ? 50% cancer further improve PCa death discrimination slightly.

Keywords: prostate cancer, prognosis, prognostic markers, Gleason score, virtual microscopy, histopathology

Plain Language Summary

The Gleason score, the most powerful prognostic factor in prostate cancer, has undergone major revisions in 2005 and 2014. While these revisions have changed clinical practice around the world, it remains unclear if they have also improved prostate cancer prognostication. Our study shows that the Gleason score revisions have indeed improved prostate cancer death prediction. We also show that other histopathological factors, including comedonecrosis, high-grade prostatic intraepithelial neoplasia and number of cores with ≥50% cancer, have potential prognostic utility beyond the Gleason score.

nature.com

SATB1, genomic instability and Gleason grading constitute a novel risk score for prostate cancer

Habermann, Jens K.

Abstract

Current prostate cancer risk classifications rely on clinicopathological parameters resulting in uncertainties for prognostication. To improve individual risk stratification, we examined the predictive value of selected proteins with respect to tumor heterogeneity and genomic instability. We assessed the degree of genomic instability in 50 radical prostatectomy specimens by DNA-Image-Cytometry and evaluated protein expression in related 199 tissue -microarray (TMA) cores. Immunohistochemical data of SATB1, SPIN1, TPM4, VIME and TBB5 were correlated with the degree of genomic instability, established clinical risk factors and overall survival. Genomic instability was associated with a GS ≥ 7 ($p = 0.001$) and worse overall survival ($p = 0.008$). A positive SATB1 expression was associated with a GS ≤ 6 ($p = 0.040$), genomic stability ($p = 0.027$), and was a predictor for increased overall survival ($p = 0.023$). High expression of SPIN1 was also associated with longer overall survival ($p = 0.048$) and lower preoperative PSA-values ($p = 0.047$). The combination of SATB1 expression, genomic instability, and GS lead to a novel Prostate Cancer Prediction Score (PCP-Score) which outperforms the current D'Amico et al. stratification for predicting overall survival. Low SATB1 expression, genomic instability and GS ≥ 7 were identified as markers for poor prognosis. Their combination overcomes current clinical risk stratification regimes.

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Radical Prostatectomy Without Prior Biopsy Following Multiparametric Magnetic Resonance Imaging and Prostate-specific Membrane Antigen Positron Emission Tomography

This article was originally published here

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ABSTRACT

A biopsy-free diagnostic pathway in prostate cancer (PC) is limited by the diagnostic accuracy of multiparametric magnetic resonance imaging (mpMRI). The improved accuracy of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) raises the question whether this imaging modality can complement mpMRI to safely avoid biopsy prior to radical prostatectomy (RP). In this case series, we report the feasibility of primary RP without prior biopsy based on a high suspicion of significant PC in both mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] score ≥4) and PSMA-PET (PET score ≥4 on a five-point Likert scale and maximum standardized uptake value ≥4.0) in 25 patients. All patients showed International Society of Urological Pathology (ISUP) grade ≥2 PC in postoperative histopathology. We report patient- and lesion-based comparisons with histopathology of the prostate specimen. Results of our case series may trigger the discussion about RP without prior biopsy as a possible option in well-selected patients. Our case series is limited by retrospective design and small sample size. We want to emphasize clearly that this practice should not be regarded as a standard procedure at the moment. Future studies with larger cohorts only inside a prospective, ethically approved study design are necessary to confirm these results.

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Incidental Prostate Cancer from Prostate with Benign Biopsies: A Predictive and Survival Analysis from Cohort Study

Authors Yang CH , Lin YS , Weng WC, Hsu CY , Tung MC, Ou YC

Purpose: This cohort was to evaluate incidental prostate cancer (iPCa) from men with preoperative benign biopsies and demonstrate their outcomes under different managements.
Patients and Methods: Between 2015 and 2017, we analyzed the risk factors having iPCa from surgical specimens from men provided with benign preoperative biopsies of their prostates. Furthermore, we compared the survival outcomes according to the different managements after iPCa was diagnosed. Receiver operating characteristic (ROC) curve was utilized to find the best thresholds. Univariable and multivariable nested logit regression were performed to estimate the effect size of different independent variables. Odds ratio (OR) was expressed with 95% confidence interval, and the alpha level was 5%.
Results: In 295 men we enrolled, there were 57 (19%) men having iPCa from surgical specimens. In univariable logit regression, we found significant variables of age, PSA, prostatic volume, PSA velocity ≥ 0.75 ng/mL/year for 3 years, taking 5α reductase inhibitors, abnormal digital rectal examination, cores of biopsy and surgical methods. In multivariable model, PSA was the strongest variable predicting iPCa (OR 3.81 [2.04– 7.07]; Wald: 17.75; $p < 0.001$). In ROC curve, the best threshold was 9.025 ng/mL (area under curve: 0.95; sensitivity: 0.947; specificity: 0.866). In Kaplan–Meier curve of 27.89-month follow-up, robot-assisted simple prostatectomy (RASP) can provide similar PSA progression-free period as robot-assisted radical prostatectomy (RARP) following transurethral surgeries in organ-confined cancer (Log rank test, $p = 0.293$), and both of them were better than external-beam radiation therapy (RT) following transurethral surgeries (Log rank test, $p < 0.001$).
Conclusion: PSA was the strongest variable to predict iPCa out of prostate with preoperative benign biopsies. RASP was parallel to RARP following transurethral surgeries in organ-confined cancer in the short term.

On the Lighter Side